Hydroxyurea for Sickle Cell Disease: A Systematic Review of Benefits, Harms, and Barriers of Utilization

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Executive Summary

1. Benefits of hydroxyurea (HU) in adults

Summary of Evidence

A single randomized trial (MSH) of 299 patients with follow up of 21 months demonstrated that compared to placebo, HU treatment was associated with lower annual rates of pain crises (median, 2.5 vs. 4.5 crises per year, P < 0.001), longer time to a first crisis (3.0 vs. 1.5 months, P = 0.01) and second crisis (8.8 vs. 4.6 months, P < 0.001), lower incidence of acute chest syndrome (25 vs. 51 patients, P < 0.001) and need for transfusions (48 vs. 73 patients, P = 0.001). Effect on mortality and stroke outcomes were not statistically significant. HU treatment was also associated with increase in hemoglobin (0.6 g/dl) and fetal hemoglobin (from 5% to 8.6% in the intervention group compared with drop in the placebo group from 5.2 to 4.7%). Costs for hospitalization for pain were lower in the HU group ($12,160 vs. $17,290; *P* < 0.05). Over two years of treatment, the benefit of HU treatment on quality-of-life measures was limited to those patients taking HU who maintained a high HbF response, compared to those with low HbF response or on placebo. These restricted benefits occurred in social function, pain recall and general health perception. Annualized total costs were similar between the two groups. When the cohort was followed up to 9 years, those taking hydroxyurea had 40% reduced mortality (this is analysis according to cumulative HU exposure and not according to the original randomization). Survival was related to HbF levels and frequency of vaso-occlusive events. The trial had adequate bias protection measures but was stopped early for benefit which may exaggerate the observed benefit.

Supporting evidence from 21 observational studies with follow up of 24–96 months was consistent showing reduction in pain crises (60%–90%) and hospitalizations (90%–100%) and increase in hemoglobin F (4%–20%). The quality of the evidence can be affected by stopping early and imprecision (single trial with <300 events) of the randomized trial but is considered overall to be high because inference is strengthened by the supporting observational evidence, the large treatment effect and the change in disease trajectory that follows administration of HU.

Evidence profile:

- **The quality of the evidence supporting the beneficial effect of HU in adults on the incidence of pain crises, acute chest syndrome, the need for transfusions, hemoglobin and fetal hemoglobin levels is HIGH.**
- **The quality of the evidence supporting HU effect on mortality and stroke is VERY LOW.**

2. Benefits of hydroxyurea (HU) in children

Summary of Evidence

A single randomized trial with cross over design (after 6 months) enrolled 25 children 2 to 22 years old (median: 9 years). HU treatment was associated with decreased hospitalizations (1.1 vs 2.8 admissions; *P* = .0016) and hospitalization days (7.1 vs 23.4 days/year; *P* = .0027), increased hemoglobin level by a 0.4 g/dL (*P* = .07) and HbF level by 10.7% (*P* < .001). The allocation in this trial was well concealed but only patients were blinded. The study used within-subject comparison and adjusted for carry-over effect but did not include a washout period. The quality of the evidence is reduced due to short follow up, methodological limitations and imprecision (single trial with <300 events), and increased due to large treatment effect.

Supporting evidence from 33 observational studies with follow up of 24–36 months was consistent (but with larger treatment effect) showing reduction in pain crises (50%–90%) and increase in hemoglobin (1 g/L) and hemoglobin F (improvement between 5% and 14%, from 4–10% to 13–22%) and decreased in hospitalizations (by 56% to 96%).

Evidence profile:

- **The quality of the evidence supporting the beneficial effect of HU on the incidence of pain crises, the need for transfusions, occurrence and duration of hospitalization, hemoglobin and fetal hemoglobin levels is MODERATE.**
- **The quality of the evidence supporting the beneficial effect on other patient important outcomes (acute chest syndrome, neurologic complications and mortality is VERY LOW.**

Subgroup analyses

HU Dosing

Three observational studies (enrolling over 200 patients) used HU maximum tolerated dose (MTD) in adults, while 9 studies (enrolling over 400 patients) used lower dosing. Studies that used MTD reported a 2-4 fold improvement in the percentage of HbF compared with baseline level and a about 10% increase in hemoglobin and a significant decrease in the incidence of pain crises and/or hospitalization rates (up to 95% decrease). The outcomes reported in studies with lower dosing were less consistent. Effect on hemoglobin and the percentage of HbF was comparable to MTD in some studies (n = 4) and inconclusive in others (n = 2), and effect on pain crises/hospitalizations was reported in only 2 studies.

Seventeen studies (enrolling over 1,100 patients) used HU MTD on children, while 8 studies (enrolling just over 500 patients) used lower dosing. Studies that used MTD reported a 2-4 fold improvement in the percentage of HbF compared with baseline level. In studies using lower doses, this increase was lower (1-2 folds). Hospitalization rates and pain crises incidence were poorly reported in these studies.

Genotypes

Observational studies mainly enrolled patients with Hb SS genotype. Other genotypes were occasionally included; however outcomes were mostly reported for the entire cohort. Two studies reported outcomes stratified per genotype, both in adults.[1, 2] In adults with adult sickle β-thalassemia, HbF increased from 6.0% to 34.7% to 8.1% to 42.2; which is similar to increase in SS patients. Effect on pain crises and toxicity was also similar (sample size is small). Similar trend is found in another study that enrolled 55 patients with sickle cell/β thalassemia.

3. Harms of HU

Summary of Evidence

Toxicity evidence in SCD is derived from 2 RCTs that enrolled 324 subjects and 47 observational studies that enrolled over 3,000 subjects. In non SCD, harm evidence is derived from 21 RCTs that enrolled over 4,800 subjects and 35 observational studies that enrolled over 7,500 patients.

Evidence profile:

- **The quality of evidence supporting an association of HU treatment with reversible bone marrow suppression is HIGH. The significance of this outcome in terms of patient/clinical importance was variable**
- **The available evidence does not support association of HU treatment with leukemia in adults or children with overall quality that is LOW.**
- **The available evidence does not support association of HU treatment with leg ulcers in adults (MODERATE) or children (LOW).**
- **Numerous other side effects were reported but none with certain causality (VERY LOW).**
- **Minimal human data exist on the reproductive effects of hydroxyurea in males and females.**

4. Barriers to sickle cell disease patient care

Summary of Evidence

Data regarding barriers to the use of HU are minimal. Most of the available data reported barriers and facilitators of the overall care of SCD in general. Inference from these data can be generalized to the use of HU when appropriate.

A total of 25 studies that enrolled over 4,700 subjects contributed to this analysis. Two studies focused exclusively on adults, 18 on children and 5 studies included both. Studies that were surveys of self-reported perceived barriers (26 studies) identified: (1) lack of knowledge about disease, (2) negative provider attitudes, (3) race, (4) insufficient explanation of HU risks/benefits by providers, (5) brief time spent by providers on counseling, (6) Loss of medication, and (7) providers' reluctance to prescribe pain medication.

The interventions that were associated with improvement in the care of SCD patients (16 studies) were: (1) the implementation of a protocol/clinical pathway, (2) educational programs and (3) adherence monitoring support systems. However, these results were quite heterogeneous.

Evidence profile:

- **VERY LOW quality evidence supports the identification of barriers and the efficacy of interventions aiming at overcoming barriers due to heterogeneity of studies' design and results, and the observational nature of evidence**

Included Studies

Table 1. Description of Randomized Controlled Trials Investigating the Efficacy of Hydroxyurea Treatment for Sickle Cell Disease

Author, year	Location	Design	Recruitment start date - end date	Inclusion and exclusion criteria	Intervention: Starting dose—titration dose	Planned duration of treatment	Quality score
Adults-MSH: Ballas, 2006[3]	North America	RCT	Jan 1992 - Apr 1993	Inclusion: Age >18; SCA; Hb Sα+ thal, Pain >3/yr Exclusion: Hb Sß+ thal; ß0 thal; SC; xfuse dependant; Preg; Op; SA; CTA; stroke in last 6 years; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding	HU: 15 mg/kg/day—Increased 5 mg/kg every 12 weeks if ANC ≥2000, retic and platelets ≥80,000/ul, and Hb ≥4.5 g/dl Placebo: Escalation per Data Coordinating Center (random)	2 years	4
Adults-MSH: Ballas, 2009[4]	North America	RCT	Jan 1992 - Apr 1993	Inclusion: Age >18; SCA; Hb Sα+ thal, Pain >3/yr Exclusion: Hb Sß+ thal; ß0 thal; SC; xfuse dependant; Preg; Op; SA; CTA; stroke in last 6 years; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding	HU: 15 mg/kg/day—Increased 5 mg/kg every 12 weeks if ANC ≥2000, retic and platelets ≥80,000/ul, and Hb ≥4.5 g/dl Placebo: Escalation per Data Coordinating Center (random)	2 years	4
Adults-MSH: Charache, 1995[5]		RCT	Jan 1992 - Apr 1993	Inclusion: Age >18; SCA; Hb Sα+ thal, Pain >3/yr Exclusion: Hb Sß+ thal; ß0 thal; SC; xfuse dependant; Preg; Op; SA; CTA; stroke in last 6 years; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding		2 years	5
Adults-MSH: Charache, 1996[6]			Jan 1992 - Apr 1993	Inclusion: Age >18; SCA; Hb Sα+ thal, Pain >3/yr Exclusion: Hb Sß+ thal; ß0 thal; SC; xfuse dependant; Preg; Op; SA; CTA; stroke in last 6 years; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding		2 years	4

Table 1. Description of Randomized Controlled Trials Investigating the Efficacy of Hydroxyurea Treatment for Sickle Cell Disease (continued)

Author, year	Location	Design	Recruitment start date - end date	Inclusion and exclusion criteria	Intervention: Starting dose—titration dose	Planned duration of treatment	Quality score
Adults-MSH: Hackney, 1997[7]		RCT	Jan 1992 - Apr 1993	Inclusion: Age >18; SCA; Hb Sα+ thal, Pain >3/yr Exclusion: Hb Sß+ thal; ß0 thal; SC; xfuse dependant; Preg; Op; SA; CTA; stroke in last 6 years; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding		18 months	3
Adults-MSH: Moore, 2000[8]			Jan 1992 - Apr 1993			2 years	4 (Quality Deficiency: No description of withdrawals or dropouts.)
Adults-MSH: Steinberg, 1997[9]			Jan 1992 - Apr 1993			2 years	4
Adults-MSH: Steinberg, 2003[10]		Cohort (f/u of MSH)				2 years	Observational Study
Adults-MSH: Steinberg, 2010[11]		Cohort (f/u of MSH)				2 years	Observational Study
Pediatric-Belgian Trial: Ferster, 1996[12]	Europe	Cross-over	June 1992 - Dec 1993	Inclusion: SCA, Hb Sα+ thal; 3/yr pain episodes, stroke; acute chest; splenic sequestration **Exclusion**: Hb Sß+ thal; Hb S ß0 thal	HU: 20mg/kg/day—Increased by 5mg/kg/day after 2 months, if no response increased to 25 mg/kg Placebo: Not described	HU: 6 months Placebo: 6 months	3

ANC = absolute neutrophil count; CTA = concurrent treatment with an anti-sickling agent; f/u = follow up; Hb Sß+ thal = sickle ß+ thalassemia; Hb S ß0 thal = Sickle ß0 thalassemia; Hb Sα+ thal = Sickle α+ thalassemia; HbA = hemoglobin A; HIV = Human Immunodeficiency Virus; HU = hydroxyurea; MSH = Multicenter Study of Hydroxyurea for Sickle Cell Anemia; Op = opioid use; Pain = pain episode; Preg = pregnancy; RCT = Randomized controlled trial; retic = reticulocytes; SA = substance abuse; SC = SC genotype; SCA = sickle cell anemia; xfuse = transfusion dependant.

Table 2. Quality of Randomized Controlled Trials of HU in Sickle Cell Disease

RCT	Blinding: Patients	Blinding: Outcome Assessors	Blinding: Data Collectors	Blinding: Data Analysts	Blinding: Care Givers	Allocation concealment	Loss to follow-up described	Discontinued trial
MSH[5]	Yes	Yes	Yes	NR	Yes	Probably yes	No	Yes
Belgian trial[12]	Yes	No	No	No	No	Probably yes	Yes	No

MSH: Multicenter Study of hydroxyurea.

Table 3. Description of Patient Populations in Randomized Controlled Trials Concerning the Efficacy of Hydroxyurea in Sickle Cell Disease

Author, year	Patient groups Intervention (N)	Recruitment start date-end date	Mean Age	% Male	Race, n	Genotype/haplotype, n (%)	Last observation
MSH: Ballas, 2006[3]	HU (141) Placebo (136)	Jan 1992-April 1993				SS (100)	24 months
MSH: Ballas, 2009[4]	HU (16) Non HU (33) Unknown HU exposure (45)	Jan 1992-April 1993	27 (females), 29.8 (males)	45	NR	SS (100)	17 years
MSH: Charache, 1995[5]	HU (152) Placebo (147)	Jan 1992- April 1993	HU: 30 Placebo: 31	HU: 49 Placebo: 48	HU: Black Non-Hispanic, 149 Black Hispanic, 1 Other, 2 Placebo: Black Non-Hispanic, 142; White Hispanic, 2 Other, 3	HU: SS, 151; Hb Sßo thal, 1 Benin/Benin, (36); Benin/CAR, (21); Benin/Senegal, (3); Senegal/CAR, (3), Other (23) Placebo: SS, 145; Hb Sßo thalassemia, 2, Benin/Benin, (43); Benin/CAR, (20); Benin/Senegal, (3); Senegal/CAR, (3), Other (17)	28 months
MSH: Charache, 1996[6]	HU (152) Placebo (147)	Jan 1992-April 1993	HU: 30 Placebo: 31	HU: 49 Placebo: 48	HU: Black Non-Hispanic, 149 Black Hispanic, 1 Other, 2 Placebo: Black Non-Hispanic,142 White Hispanic, 2 Other, 3	HU: SS, 151; Hb Sßo thal, 1 Benin/Benin, (36); Benin/CAR, (21); Benin/Senegal, (3); Senegal/CAR, (3), Other (23) Placebo: SS, 145; Hb Sßo thal, 2, Benin/Benin, (43); Benin/CAR, (20); Benin/Senegal, (3); Senegal/CAR, (3), Other (17)	HU: Mean 28±6 months Placebo: Mean 28±7 months
MSH: Hackney, 1997[7]	HU (10) Placebo (14)	Jan 1992- April 1993	HU: 30.5 Placebo: 29.8	HU: 60 Placebo: 57		SS (100)	18 Months
MSH: Moore, 2000[8]	HU (152) Placebo (147)	Jan 1992- April 1993	HU: 30 Placebo: 31	HU: 49 Placebo: 48			NR
MSH: Steinberg, 1997[9]	HU (152) Placebo (147)	Jan 1992-April 1993	HU: 30 Placebo: 31				Mean 28 months (range = 21–38)

Table 3. Description of Patient Populations in Randomized Controlled Trials Concerning the Efficacy of Hydroxyurea in Sickle Cell Disease (continued)

Author, year	Patient groups Intervention (N)	Recruitment start date-end date	Mean Age	% Male	Race, n	Genotype/haplotype, n (%)	Last observation
MSH: Steinberg, 2003[10]	HU (152) Placebo (147)	Jan 1992-April 1993					HU: 7.7 years Placebo: 7.4 years
MSH: Steinberg, 2010[11]	Never on HU (44) HU < 5 yrs (140) HU 5-10 yrs (55) HU 10-15 yrs (40) HU > 15 yrs (20)	Jan 1992-April 1993		Never on HU: 47.7 HU < 5 yrs: 43.6 HU 5-10 yrs: 60 HU 10-15 yrs: 50 HU > 15 yrs: 55			17.5 years
Belgian trial: Ferster, 1998[12]	HU (25)	June 1993- Dec 1993	Median, 9; Range, 2-22	48	Black Non-Hispanic, 25	SS, 25	12 months

CAR = Central African Republic; Hb = hemoglobin; Hb Sß° thal = Sickle ß° thalassemia; HU = hydroxyurea; MSH = Multicenter Study of Hydroxyurea for Sickle Cell Anemia; NR = not reported; SS = Sickle Hemoglobin SS Disease.

Table 4. Efficacy Results of Randomized Controlled Trials in Sickle Cell Disease

Author, year	Intervention (N)	Mean durations of drug and followup	Deaths, n (%)	Hb F, % ± SD	F cells, % ± SD	Hemoglo-bin, g/dl	MCV, fl ± SD	Reticulocyte count, k/ul	Weight change, kg (%)	Change in peak power, watts ± SEM	Pain crises & admissions	Transfusion
MSH: Ballas, 2006[3]	HU (141) Placebo (136)	HU: 24 months Placebo: 24 months										
MSH: Charache, 1995[5]	HU (152) Placebo (147)	HU: 24 months Placebo: 28 months		HU: 8.6± 6.8 Placebo: 4.7± 2.2		HU: 9.1± 1.5 Placebo: 8.5± 1.3		HU: 231± 100 Placebo: 300± 99	HU: (3) Placebo: (6)		HU: ACS, 25# Placebo: ACS, 51††	HU: 48** Placebo: 73‡‡††
MSH: Charache, 1996[6]	HU (152) Placebo (147)	HU: 24 months Placebo: 28 months ± 6	HU: 2 Placebo: 5 or 6									HU: 55‖ Placebo: 79¶
MSH: Hackney, 1997[7]	HU (10) Placebo (14)	HU: 24 months Placebo: 18 months							HU: 3.2± 0.8† Placebo: 1.8± 0.8‡	HU: 104.9± 31 Placebo: 57.7± 20		
MSH: Moore, 2000[8]	HU (152) Placebo (147)	HU: 24 months Placebo: NR										
MSH: Steinberg, 1997[9]	HU (152) Placebo (147)	HU: 24 months Placebo: 28 months (range, 21-38)		HU: 3.6± 5.4§ Placebo: -0.4± 2§	HU: 15.2± 17.3§ Placebo: 2.3± 7.1§		HU: 9.7± 11.2§ Placebo: -0.4, ± 4.8§	HU: 97± 107§ Placebo: 21± 72§				
MSH: Steinberg, 2003[10]	HU (152) Placebo (147)	HU: 7.7 years Placebo: 7.4 years	HU: 36 (23.7) Placebo: 39 (26.5)								HU: Stroke, 8* Placebo: Stroke, 6*	

Table 4. Efficacy Results of Randomized Controlled Trials in Sickle Cell Disease (continued)

Author, year	Intervention (N)	Mean durations of drug and followup	Deaths, n (%)	Hb F, % ± SD	F cells, % ± SD	Hemoglo-bin, g/dl	MCV, fl ± SD	Reticulocyte count, k/ul	Weight change, kg (%)	Change in peak power, watts ± SEM	Pain crises & admissions	Transfusion
MSH: Steinberg, 2010[11]	Never on HU (44) HU < 5 yrs (140) HU 5-10 yrs (55) HU 10-15 yrs (40) HU > 15 yrs (20)	Never on HU: 17.5 years HU < 5 yrs: 17.5 years HU 5-10 yrs: 17.5 years HU 10-15 yrs: 17.5 years HU > 15 yrs: 17.5 years	Never on HU: 16 (36) HU < 5 yrs: 78 (56) HU 5-10 yrs: 26 (47) HU 10-15 yrs: 9 (23) HU > 15 yrs: 0 (0)									
Other controlled trial: Ferster, 1998[12]	HU (22) Placebo (22)	HU: 6 months Placebo: 22 months		HU: 10.8§ §§		HU: 0.4§ ‖ ‖	HU: 10.41 § §§	HU: -46§ §§			HU: 1.1¶¶ Placebo: 2.8##	

* Stroke
† Mean ± SEM, p = <0.005
‡ (Mean ± SEM)
§ Change from baseline, mean ± SD where applicable.
‖ Patients, P = 0.002, RBC units transfused, 423 P = 0.002
¶ Patients, RBC units transfused, 670.
# p < 0.001, Median time to first crisis, 3 months, p < 0.01, Pain crises per year, 2.5 (OR 0.6-7).
** p < 0.001, RBC units transfused, 336.

†† Median time to first crisis, 1.5 months. Pain crises per year, 4.5 (IQR 2-10.2)

‡‡ RBC units transfused, 586 §§ p < 0.001 ‖ ‖ p = NS ¶¶ p = 0.016, Days hospitalized, 3.6, p = 0.0027, hospitalizations per year ## Days hospitalized, 11.7, hospitalizations per year

ACS = acute chest syndrome; HbF = Fetal hemoglobin; HU = hydroxyurea; IQR = interquartile range; MCV = mean corpuscular volume; MSH = Multicenter Study of Hydroxyurea for Sickle Cell Anemia; NR = not reported; OR = odds ratio; RBC = red blood cells; SD = standard deviation; SEM = standard error of the mean.

Table 5. Toxicity Results in Randomized Controlled Trials of Hydroxyurea Treatment in Sickle Cell Disease

Author, year	Intervention (N)	Mean drug duration	Death, n (%)	Thrombocytopenia	Neutropenia, %	Absolute neutrophil count, ul +/SD	% GI disturbance,	% Rash or Nail changes	Lower extremity ulcers	Other
MSH: Ballas, 2009[4]	HU (16) Non HU (33) Unknown HU exposure (45)	NR								Study conducted to assess HU exposure effects on abortion for female patients and female partners of male patients. Authors concluded that exposure of the fetus to HU does not cause teratogenic changes in pregnancies that terminate in live birth (full term or premature)
MSH: Charache, 1995[5]	HU (152) Placebo (147)	HU: 24 months Placebo: 28 months	HU: (2) Placebo: (5)	HU: 4 Placebo: 5		HU 4,900± 2,000 Placebo: 6,400± 2,000			HU: 15 Placebo: 17	HU: Hemoglobin > 12.8 g/dl, 11 Platelets > 800,000/ul, 4 Placebo: Hemoglobin > 12.8 g/dl, 1 Total Bilirubin > 10 mg/dl, 4

Table 5. Toxicity Results in Randomized Controlled Trials of Hydroxyurea Treatment in Sickle Cell Disease (continued)

Author, year	Intervention (N)	Mean drug duration	Death, n (%)	Thrombocytopenia	Neutropenia, %	Absolute neutrophil count, ul +/SD	% GI disturbance,	% Rash or Nail changes	Lower extremity ulcers	Other
MSH: Charache, 1996[6]	HU (152) Placebo (147)	HU: 24 months Placebo: 28 months ± 6	HU: (2) Placebo: (6)		HU: 66		HU: 59 Placebo: 58	HU: 25 Placebo: 25	HU: 15 Placebo: 17	HU: Hair Loss, 18 Fever, 91 Aplastic crisis, 1 Aseptic Necrosis, 9 Lymphadenopathy, 45 Bleeding Tendency, 7 Placebo: Hair Loss, 28 Fever, 96 Aplastic crisis, 5 Aseptic Necrosis, 9 Lymphadenopathy, 56 Bleeding Tendency, 3
MSH: Steinberg, 1997[9]	HU (152) Placebo (147)	HU: 24 months Placebo: 28 months (range,21-38)				HU: 1,900* ± 2,400 Placebo: 400 ± 2,200				
MSH: Steinberg, 2003[10]	HU (152) Placebo (147)	HU: NR 7.7 years Placebo: NR 7	HU: 36 (23.7) Placebo: 39 (26.5)							HU: Malignancy, 1 Sepsis/Infection, 18 Hepatic Failure, 3 Renal Failure, 14 Placebo: Malignancy, 1 Sepsis/Infection, 20 Hepatic Failure, 10 Renal Failure, 14

Table 5. Toxicity Results in Randomized Controlled Trials of Hydroxyurea Treatment in Sickle Cell Disease (continued)

Author, year	Intervention (N)	Mean drug duration	Death, n (%)	Thrombocytopenia	Neutropenia, %	Absolute neutrophil count, ul +/SD	% GI disturbance,	% Rash or Nail changes	Lower extremity ulcers	Other
MSH: Steinberg, 2010[11]	Never on HU (44) HU < 5 yrs (140) HU 5-10 yrs (55) HU 10-15 yrs (40) HU > 15 yrs (20)	Never on HU: None HU < 5 yrs: HU 5-10 yrs: HU 10-15 yrs: HU >15 yrs:	Never on HU: 16 (36) HU < 5 yrs: 78 (56) HU 5-10 yrs: 26 (47) HU 10-15 yrs: 9 (23) HU >15 yrs: 0 (0)							Never on HU: Stroke: 0 Renal dz: 9 Hepatic dz: 5 Malignancy: 0 Infection: 3 HU < 5 yrs: Stroke: 12 Renal dz: 27 Hepatic dz: 9 Malignancy: 1 Infection: 27 HU 5-10 yrs: Stroke: 3 Renal dz: 10 Hepatic dz: 3 Malignancy: 2 Infection: 15 HU 10-15 yrs: Stroke: 0 Renal dz: 5 Hepatic dz: 1 Malignancy: 0 Infection: 10 HU >15 yrs: Stroke: 3 Renal dz: 1 Hepatic dz: 0 Malignancy: 0 Infection: 0
Belgian Study: Ferster, 1998[12]	HU (25)	6 months 22 months	6 months: 2 22 months: 0							6 months: No clinically significant toxicity

* Change from baseline, mean ± SD GI = gastrointestinal; HU = hydroxyurea; NR = not reported; SD = standard deviation

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Al-Jam'a, 2002[13]	Middle East	Adults-Children-prospective	Efficacy	To assess the efficiency and safety of HU in patients with SCD from the Eastern Province, Kingdom of Saudi Arabia	**Inclusion**: Age, >5 years, SCA, Hb Sß+ thal, Hb Sß0 thal, S α+ thal, pain ≥ 4 admissions for VOC in past year **Exclusion**: Trans, Preg, renal failure, abnormal renal tests, liver failure, abnormal hepatic function tests, HIV+, progesterones other than in OCPs, theophyllines, androgens, estrogens	500 mg/day, 500 mg QOD if wt <50 kg: 500 mg each month until MTD or 35 mg/kg reached	18.5 [12 to 49]	89
Ataga, 2006[14]	North America	Adults-prospective	Effectiveness	To evaluate the trends of development of pulmonary hypertension, the association of pulmonary hypertension with clinical and laboratory measures and the effect of pulmonary hypertension on mortality in SCD patients	**Inclusion**: SCA, Hb Sß+ thal, Hb Sß0 thal, S α+ thal, SC **Exclusion**: ACS in last 4 weeks, current crisis or acute illness	NR	NR	40
Bakanay, 2005[15]	North America	Children-Retro-spective	Effectiveness	To report on the demographic, clinical and laboratory characteristics of a group of patients who died of complications while on HU therapy compared with HU-treated surviving patients	NR	15 mg/kg/day: 5mg/kg as tolerated	36 [5-78]	50

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Berthaut, 2008[16]	Europe	Adult males, retrospective	Toxicity	To investigate the toxicity of HU on sperm parameters and fertility	**Inclusion**: SCD males	20-30 mg/kg/day		33
Chaine, 2001[17]	Europe	Adult-retro-spective	Toxicity	To evaluate the risk of cutaneous adverse reactions in SCD patients treated with HU	**Inclusion**: adult, SCA, Hb Sß+ thal, Hb Sß0 thal, S α+ thal, SC, on HU††	14-28 mg/kg/day	12 (MTD plus time to escalate)	52
Charache. 1992[18]	North America	Adults-prospective	Efficacy	To assess pharmacokinetics, toxicity, and increase in fetal Hb production in response to daily doses of HU in patients with SCA	**Inclusion**: Age >18 years, SCA, S α+ thal, pain admissions >1 in last year (including ED visits) **Exclusion**: Hb Sß+ thal, Hb Sß0 thal, Trans, preg, renal failure, abnormal renal function tests, liver failure, abnormal hepatic function tests, HIV+, AST > 100 U/L, albumin <3 g/dl, theophylline containing drugs, androgens, estrogens, or progesterones (other than birth control)	10 - 20 mg/kg/d depending on AUC at 6 hours: Increase 5 mg/kg/d Every 8 weeks	9 [0-25]	89
Cummins, 2003[19]	Europe	Adults-prospective ‖ ‖	Efficacy	To compare patients with SCD treated with cognitive behavioral therapy with patients treated with HU in terms of quality of life, pain experience, health service utilization, and pain coping strategies	**Inclusion**: Age, adult, SCA, Hb Sß+ thal, Hb Sß0 thal, S α+ thal, SC	Weight-based	23 [12-39]	37

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Dahoui, 2010[20]	Middle East	Children, adults, cross-sectional	Prevalence of comorbidity	Prevalence of pulmonary HTN in SCD pts	**Inclusion:** hemoglobins SS, Sß^{othal} and Sß$^{+thal}$	HU initiated at 10-15 mg/kg/day then increased until reaching adequate clinical response	56***	44
de Montalembert, 1997[21]	Europe	Children-prospective	Efficacy	To observe the safety and efficacy of HU in previously severely ill children with SCD	**Inclusion**: Age, 4 to20 years, SCA, Hb Sß+ thal, Hb Sß0 thal, S α+ thal, SC, Pain ≥ 3 hospitalizations in last year **Exclusion**: HIV+, renal insufficiency CrCL <120ml/1.73 m^2/min, iron deficiency or current iron supplementation, history of frequent and severe infections, monthly f/u would be difficult, hypersplenism, hepatic insufficiency (ALT > 5xULN, or chronic hepatic disease)	20 mg/kg/day 4 days/week: Increase 5 mg/kg/day every 4 weeks to a max dose of 40 mg/kg/day	32 [12 to 59]	85
de Montalembert, 1999[22]	Europe	Children-prospective	Toxicity	To evaluate the tolerance of HU in children affected with SCD	**Inclusion**: 2-20 years when starting HU	NR	22 [0.5-93]	18
de Montalembert, 2006[23]	Europe	Children-prospective	Toxicity	To asses the tolerability of HU treatment in 225 children with SCD	**Inclusion**: Pain ≥ 3 admissions, stroke and unable or refused transfusion, ACS, recurrent severe chronic anemia Hb < 6-7, high TCD velocity, cardiac ischemia	20 mg/kg/d 4 d/wk, then 4 to 7 d/wk from 1997-2003: Up to 40 mg/kg/d, increased up to 40 mg/kg/d if no response after 6 months	46 [0-152]	71
el-Hazmi, 1992[24]	Middle East	Adults-prospective	Efficacy	To assess the effectiveness of HU in managing severe forms of SCD	NR	20mg/kg/day: no titration	3	57

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Ferguson, 2002[25]	North America	Adults-retro-spective‡‡	Effectiveness	To assess the efficacy of HU in settings outside a clinical trial with longer follow-up	**Inclusion**: Age, adults, SCA, treated at two hospitals **Exclusion**: Hb Sß+ thal, Hb Sß0 thal, Sα+ thal, SC, Trans, Preg, SA, stroke in past 6 years	Every 8 weeks. Dosing based on MSH model	21.6 [3-60]§§	57
Ferster, 2001[26]	Europe	Children-prospective	Effectiveness	To evaluate the long-term efficacy and toxicity of HU in the Belgian registry of HU-treated SCD patients	**Inclusion**: Age, children and young adults, Pain ≥ 2 admissions/year, or stroke, or TIA, or ACS, or priapism, ischemic bone	20mg/kg: 5mg/kg at will of doctor¶	42	63
Flanagan, 2010[27]	North America	Children, prospective	Effectiveness	To investigate the effect of HU on production of micronuclei (MN) in red blood cells	**Inclusion**: children with SCD	25 mg/kg/d, escalating to maximum tolerated dose (MTD)	24	39
Gordeuk, 2009[28]	USA	Children, young adults, Cross-sectional	Effectiveness	The role of HU and HbF in protecting from pulmonary HTN	**Inclusion:** Age: 3-22 yrs, HbSS, HbSC, HbSß^{thal}	NR	24	38
Gulbis, 2005[29]	Europe	Children-prospective	Effectiveness	To assess the efficacy and safety of HU	**Inclusion**: Age, children and young adults, Pain ≥ 2 admissions/year, or stroke, or TIA, or ACS, or priapism, or ischemic bone	20mg/kg: 5mg/kg at will of doctor	47#	54
Hanft, 2000[30]	North America	Adults and Children-retrospective	Toxicity	To investigate the mutagenic and carcinogenic potential of long-term HU use in patients with SCD or MPDs	**Inclusion**: SCA, MPD, abnormal TCD, cardiac ischemia	NR	up to 180	31

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Hankins, 2005[31]	North America	Children-prospective	Efficacy	To study the long-term efficacy and toxicity of HU on infants, and to define the role of HU in preventing organ dysfunction	**Inclusion**: enrolled in HUSOFT§	20mg/kg: 5mg/kg every 6 months to max 30mg/kg	58.8 [25-72]	67
Hankins, 2007[32]	North America	Children-prospective	Effectiveness	To investigate the effects of HU on spleen and brain through retrospective data review of children with SCD treated with HU	**Inclusion**: children, SCA, Hb Sß0 thal	15-20 mg/kg/day: Every 8weeks to 30-35mg/kg¶¶	29 [2-103]	43
Hankins, 2008[33]	North America	Children, retrospective	Effectiveness	To evaluate the effect of HU in the Preservation of Spleen and Brain Function in children with SCD	**Inclusion**: children with HbSS or Hb SB-thalassemia, on HU, and preformed either LS scan or brain MRI/MRA	15–20 mg/kg/day, increased to a (MTD) that did not exceed 30–35 mg/kg/day, Dose escalation occurred at 8-week intervals over a 6-month period	36 months	63
Harrod, 2007[34]	North America	Children-prospective	Toxicity	To quantitate Howell-Jolly Bodies in a large cohort of children with SCD and analyze according to sicklegenotype, age, splenectomy status, and HU exposure	**Inclusion**: <20 years **Exclusion**: Hb Sß+ thal, Hb Sß0 thal	NR	NR	39
Helton, 2009[35]	USA	Children Cross-section	Efficacy	To evaluate cerebral blood flow in grey and white matter of children with SCD	**Inclusion:** Children, HbSS **Exclusion:** children requiring sedation to undergo MRI	NR	N/A	64

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Italia, 2009[2]	South Asia	Children, adults Prospective	Efficacy	To examine the efficacy of HU on adults and children with SCD and adult sickle ß-thal dz	**Inclusion:** frequent vaso-occlusive crises (>5/yr), CNS affected at least once in the past, acute chest syndrome > twice in the past, avascular necrosis of femoral head along with any of the above	10-15mg/kg/day	24	75
Khayat, 2006[36]	Central or South America or Mexico	Adults & children, retrospective	Toxicity	To determine the frequency of chromosome aberrations and the mitotic index as a criteria for evaluation of the genotoxicity and cytotoxicity of HU in SCD patients	NR	25mg/kg/d	12	27
Kinney, 1999[37]	North America	Children-prospective	Toxicity	To determine the safety and efficacy of HU in pediatric patients with SCA. This is the phase I/II HUG KIDS study- goal was to establish MTD	**Inclusion**: 5-15 years, SCA, pain ≥ 3/yr or ACS episodes in last year, 6 documented heights and weights for at 2 years preceding enrollment **Exclusion**: Trans, preg, renal failure, liver failure, sepsis, ALT > 2, HIV+, theophyline containing drugs, estrogen, Ca-blockers	15mg/kg/d: Up 5mg/kg for 8 wks up to 30mg/kg	Up to 24	86
Kratovil, 2006[38]	North America	Children-prospective	Efficacy	To determine if HU therapy affected transcranial Doppler velocities and whether changes in velocities could be associated with changes in hematologic parameters	**Inclusion**: SCA, Pain >5/year, stroke and not transfused, 2nd alloantibodies, or poor chelation, severe ACS, TCD exam before and during HU **Exclusion**: Trans, none in 6 months, SA, drugs	15 mg/kg/day: 5 mg/kg/day every 8 weeks to max of 30-25 mg/kg/day or 2000 mg/day or MTD	[6-48]	73

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Lefevre, 2008[39]	Europe	Children, retrospective	Effectiveness	To evaluate the effect of HU in prevention of stroke in children with SCD	**Inclusion**: children with SCD with TCD preformed within last 25 years	NR, not MTD	NR	33
Little, 2006[40]	USA	Adults, retrospective	Safety and efficacy	To evaluate toxicity and safety of concomitant use of HU and erythropoietin	**Inclusion**: HbSS, HbSC, adults.	HU:7.9-24.5mg/kg/d EPO: >963 (>327 to 2718) U/Kg/week in group A (high-risk, HU intolerant) pts, and >589 (>107 to 734) U/Kg/week in group B (high-risk, relative renal insufficiency) pts.	16 [11+ - 34+]	75
Loukopoulos, 1998[41]	Europe	Adults-retrospective	Efficacy	To report on the effectiveness of HU in patients with thalassemia--a report of a physician's experiences	**Inclusion**: Age, adults, Hb Sß+ thal, Hb Sß0 thal	20 mg/kg/day: no titration	NR	23
Loukopoulos, 2000[1]	Europe	Adults-prospective	Efficacy	To report on a clinical trial of HU in 55 Greek-origin patients with sickle cell/B thalassemia and patients with homozygous HbS disease who had been treated with HU for several years	**Inclusion**: Age ≥ 17 years, SCA, Hb Sß+ thal, Hb Sß0 thal, pain ≥ 3/yr, severe disease (e.g. stroke, hyperbiliuremia) **Exclusion**: pregnancy or intention to conceive	15mg/kg/day for 4 days week then 25 mg/kg/day: Titrate up to 25mg/kg/d stable for 6mos and taper to 1.0g daily	[6-48]	63

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Lukusa, 2009[42]	Europe	Adults, Cross-sectional	Toxicity	Study the effects of HU and bone marrow transplant on semen variables and hormone profiles	**NR**	20 mg/kg/day	HU: median: 126 [96-180] HSMT: median: 186 [96-252]	50
Maier-Redelsperger, 1998[43]	Europe	Children-prospective	Efficacy	To study the cellular and molecular responses to long-term HU treatment in 29 severely affected young patients with SCD	**Inclusion**: Pain **Exclusion**: Preg, renal failure, renal function within normal limits, liver failure, ALT > 1.5 ULN, HIV+, hx of severe infections, iron deficiency	20mg/kg/d 4 d/wk: Increase 5mg/kg/d monthly to max 40 ‖	22 [12 to 36]	77
Marsenic, 2008[44]	North America	Children, prospective			**Inclusion**: SCD Stable patients			44
McKie, 2007[45]	North America	Children, prospective	Effectiveness	To define the age of onset of microalbuminuria and proteinuria in children with SCD and evaluate their association with age, sex, and hemoglobin levels, Also to explore the safety and utility of HU and ACEI in prevention and treatment of sickle cell nephropathy	**Inclusion**: Age, >2 and <21 years, SCA	15-30 mg/kg/day: Based on clinical responses, MCV, HbF	21.8	50
Odievre, 2008[46]	Europe	Children, cross-sectional	Effectiveness	To investigate the effect of HU on red blood call adhesion molecules	**Inclusion**: children, HbSS	20-25 mg/kg/day		39

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Olivieri, 1998[47]	North America	Children-prospective	Toxicity	To monitor compliance with treatment of HU and evaluate the impact of HU on splenic function in children with SCD	**Inclusion**: SCA, Pain ≥3 in the previous yr, ACS, any episode in the previous yr **Exclusion**: Neutropenia, Trans, Preg, SA or severe psychologic disease interfering with accurate reporting of pain, renal failure, liver failure, ALT > x2UNL, untreated folate or iron deficiency, thrombocytopenic conditions	12.9 ± 2.7 mg/kg/d, reduced to 10mg/kg/d later: Dose increased by 5 mg/kg q 812 wks until ANC <2,000/ ml, retic <80,000/ml, plt <100k/mcL, or Hb more than 2g/dL below steady state	18	88
Pashankar, 2008[48]	USA	Children Prospective	Efficacy	To prospectively follow up on SCD patients who have pulmonary HTN and indentify risk factors	**Inclusion:** Children, pulmonary HTN (TVR > 2.5m/s), age > 6 yrs **Exclusion:** Pulmonary valve stenosis, other structural obstruction to pulmonary flow	20 mg/kg/day	Median: 23 [19-31]	81
Puffer, 2007[49]	North America	Children, cross-sectional	Effectiveness	To examine the potential cognitive benefits of hydroxyurea in children with SCD and no history of overt stroke.	**Inclusion**: 6 to 21 years of age and SCD **Exclusion**: history of overt stroke or developmental disorders (e.g., mental retardation, cerebral palsy, etc.)	NR	NA	44
Rigano, 2001[50]	Europe	Adults-prospective	Efficacy	To evaluate the efficacy of HU in a group of 22 Sicilian patients with BS/B-thal by studying the incidence of crises, frequency of hospitalization, complications and mortality	**Inclusion**: Sicilians, ≥ 3 sickle crises (any type) in previous year **Exclusion**: HIV+, bone marrow hypoplasia	15 mg/kg/day: Increased after 3 months if no response	>24	70

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Santos, 2002[51]	Central, South America	Children-prospective	Effectiveness	To evaluate the effects of long-term therapy with hydroxyurea on recovery of splenic function	**Inclusion**: Age 3 to 22, SCA, Sß0 thal, ≥ 2 episodes of priapism or ACS, ≥ 6 painful crisis	15 mg/kg/day: every 8 weeks increase by 5 mg/kg/day to max of 30 mg/kg/day or toxicity	12 months	47
Schultz, 2003[52]	North America	Adult-retro-spective	Toxicity	To report on cases of malignancy in patients with SCD		NR	22	14
Scott, 1996[53]	North America	Children-prospective	Efficacy	To assess the safety and efficacy of HU for the treatment of severe SCD in children	**Inclusion**: Age 10 to 17 years, SCA, Hb Sß0 thal, S α+ thal, pain admissions ≥ 3/year, ACS, or priapism, contraceptive measures to prevent pregnancy **Exclusion**: abnormal renal or hepatic function, noncompliance	10-20 mg/kg/day: 5 mg/kg/day Every 12 weeks	43.6 [24-63]	93
Singh, 2010[54]	India	NR, prospective	Effectiveness	to determine the efficacy of HU to treat SCD	**Inclusion**: Homozygous SCD	20 mg/kg/day, increased by 5mg/kg/day when deemed appropriate	One year	33
Svarch, 2006[55]	Central or South America or Mexico	Children retrospective	Efficacy	To demonstrate that good results can be achieved and toxicity avoided by maintaining dose of HU at 15 mg/kg/day in patients with SCD	**Inclusion**: Age, 4-18 years, SCA, Pain ≥ 3 in past year or, sepsis ≥ 1 in past 2 years **Exclusion**: ACS	15mg/kg/d: No titration	Median = 24	35
Thornburg, 2009[56]	USA	Children, Prospective	Safety and efficacy	To assess the safety and efficacy of hydroxyurea in young children with SCD and to prospectively assess kidney and brain function	**Inclusion:** Age 1.5-5 yrs, HbSS or Hb Sß0 thal	20mg/kg/day, escalating to MTD	25	75

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Thornburg, 2010[57]	USA	Children, prospective	Adherence	Association between adherence and HbF %, barriers and facilitators to adherence	**Inclusion:** children, sickle cell disease, receiving HU for at least 5 months	The mean dose at the time of the study was 24.4mg/kg/dose (range, 16.6-31.6mg/kg/dose).	55.2 [4.8-135.6]	75
Vicari, 2005[58]	Central or South America or Mexico	Adults-prospective	Effectiveness	To see if genetic determinants influence response and toxicity with HU	**Inclusion**: Age, >18 years, SCA, Pain ≥3/yr, ACS **Exclusion**: HIV+, bone marrow depression	NR, dosing similar to MSH model	30.45 [12-60]	25
Voskaridou, 1995[59]	Europe	Adults-prospective	Efficacy	To report on the response of Caucasian patients with SCD with complications of the disease (pain crises) to high "sub-toxic" doses of HU	**Inclusion**:, Hb Sß+ thal, Hb Sß0 thal, pain frequent	15 mg/kg/d, rounded up to the next 500mg 4days/wk: Increase by 5mg/kg increments, rounded up to the next 500mg q 4wks, maximal total dose of 2.5g/d**	[5-8.7]	54
Voskaridou, 2010[60]	Europe	Adults, prospective	Safety and efficacy	To evaluate efficacy and safety of HU therapy on pts with SCD	**Inclusion:** age > 16, 3+ painful attacks needing hospital/ER visits in the preceding year, presence of jaundice at presentation or complication of SCD **Exclusion:** <2 painful crises in preceding yr, presence of end-stage renal failure, pregnancy, no patient agreement on regular visits for testing and mental inability to sign forms	20 mg/kg/day single oral dose, d/c when neutrophil count < 1.5 X 10^9/L and platelet count < 100 X 10^9/L then restarted at 15 mg/kg/d increasing to 20 within 1 month. in lack of response to initial dose was incr' to 35 mg/kg/day and pts were dropped if no response was elicited after 6 months	HU: 96 [1.2-204] Non HU: 60 [1.2-216]	63

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Wang, 2001[61]	North America	Children-prospective	Efficacy	To conduct a collaborative pilot trial of HU in infants with SCA to assess (1) feasibility of administration, (2) toxicity, (3) hematologic effects, and (4) effect on spleen function‡	**Inclusion**: Age, infants-not specified by age, SCA, Hb Sß0 thal **Exclusion**: Splenomegaly, Preg, renal failure, CRCL < 120ml/min/1.73 m2, liver failure, ALT > 5n, HIV+, iron deficiency, HbA > 10% from transfusion, sig. non-sickle-related medical problem	20mg/kg: No titration	24	67
Ware, 2002[62]	North America	Children-prospective	Efficacy*	To identify predictors of Hb response in school-aged children with SCA receiving HU at MTD	**Inclusion**: Age = children, Pain ≥ 3 in past year or ≥ 3 pain and ACS episodes within 1 year of enrollment, ACS ≥3 in past 2 years **Exclusion**: renal failure, "dysfunction", liver failure	15 mg/kg/d: Increase every 8 weeks to MTD or 30mg/kg	11.7	86
Ware, 2004[63]	North America	Children-prospective	Effectiveness	To describe the clinical outcome and long-term follow-up for a cohort of pediatric patients with SCD receiving HU for prevention of secondary stroke	**Inclusion**: Age = pediatric, SCA, Trans, stroke **Exclusion**: Hb Sß+ thal, S α+ thal, S α+ thal, SC	15-20 mg/kg per day, escalating to MTD	29 [12-49]	88
Zimmerman, 2004[64]	North America	Children-prospective	Effectiveness	To investigate the long-term efficacy of HU (in improving hematologic parameters) in children with SCD receiving the MTD†	**Inclusion**: on HU for at least 6 mo, SCD	15 or 20mg/kg: Up to 30mg/kg if tolerated	45 (24) [6-10]	88

Table 6. Description of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ design	Study Goal	Objective	Inclusion and exclusion criteria	HU Starting Dose: Titration Schedule	Mean Observation Duration in Months, (SD) [range]	Q score
Zimmerman, 2007[65]	North America	Children - prospective	Efficacy	To describe a prospective, single-institution Phase II trial of HU for children with SCD and increased transcranial doppler flow velocities	**Inclusion**: Age all pediatric, SCA, S/O Arab **Exclusion**: sickle ß+ thal, sickle ßo thal, sickle α+ thal, SC	"as in routine practice": To MTD	10 (5) Median = 8	73

* Used data from the phase I/II HUG KIDS study but analyses only included children who reached MTD; 5.6% of pills were returned.
† Included patients who were in HUG-KIDS (n = 15), in HUSOFT (n = 7), and 33 patients in a secondary prevention of stroke study.
‡ Investigators matched 3 patients from CSSCD to enrolled patients by diagnosis, gender, age.
§ This was the extension study of HUSOFT. Of the 21 who completed the 2 years in HUSOFT, 17 (of the 21) completed 4 years, and 11 (of the 21) completed 6 years from start. ‖ Mean dosage 34.2mg/kg administered 4 days a week.
¶ At the end of year one of the study, 55% were on 20-25mg/kh, 41% were under 20mg/kg, 4% were on 25-30mg/kg, and 1 was on more than 30mg/kg.
# 109 patients for a total of 426 patient-yrs. The initial 109 children were followed for up to 8 years (14 children with this duration).
** The maintenance phase (after first 24 weeks) was 100mg/d for 4d/week and then patients were put into one of three arms that differed slightly in administration.
†† Recruited all adult patients who came to their institution for skin exam who had SCD and were on HU.
‡‡ Patients were stratified by duration of therapy (or completeness of therapy). Fourteen patients had previously participated in MSH study.
§§ Mean observation duration was 9.7 months in the group on HU for <24 months.
‖‖ The cross-sectional design was based on questionnaires (in 2002 for HU patients, 2000 for CBT patients) and review of records: there is a strong likelihood of selection bias.
¶¶ The median MTD was 30mg/kg/day (range 15-35 mg/kg/day).

ACEI = ACE Inhibitors; ACS = acute chest syndrome; ALT = Alanine Aminotransferase; ANC = absolute neutrophil count; AUC = area under the curve; BS/B-thal = hemoglobin S beta-thalassemia; Ca = calcium; CBT = cognitive behavioral therapy; CrCL = creatinine clearance; CSSCD = Cooperative Study of Sickle Cell Disease; ED = Emergency Department; f/u = follow up; Hb = hemoglobin; Hb Sß+ thal = Sickle ß+ thalassemia; Hb S ß° thal = Sickle ß° thalassemia; HbA = hemoglobin A; HbF = fetal hemoglobin; HbS = sickle hemoglobin; HU = hydroxyurea; HUG KIDS = pediatric hydroxyurea safety trial; HUSOFT = The Hydroxyurea Safety and Organ Toxicity trial; hx = history; MCV = mean corpuscular volume; MPD = myeloproliferative disorder; MSH = Multicenter Study of Hydroxyurea for Sickle Cell Anemia; MTD = maximum tolerated dose; NR = not reported; OCP = oral contraceptive pill; plt = platelets; Preg = pregnancy; Q = quality; QOD = 4 times a day; retic = reticulocytes; S α+ thal = sickle α+-thalassemia; S/O = hemoglobin SO Arab; SA = substance abuse; SC = Sickle-Hemoglobin C Disease; SCA = sickle cell anemia; SCD = Sickle Cell Disease; SD = standard deviation; TCD = transcranial Doppler; TIA = transient ischemic attack; Trans = transfusion; ULN = upper limit of normal; VOC = vaso-occlusive crisis; HSMT: hematopoietic stem cell transplantation; CNS: central nervous system; EPO: erythropoietin.

Table 7. Quality of Observational Studies on Hydroxyurea Use in Sickle Cell Disease*

Author, year	Study description	Inclusion or exclusion criteria described	Key characteristics of participants described	Intervention described	Adherence to the drug described	Adjusted or stratified estimate of the treatment effect provided	Reported ≥1 objective outcomes	Reported # participants lost to follow-up	Q score
Al-Jam'a, 2002[13]	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2		Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	89
Ataga, 2006[14]	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 1	Rev. #1: 1 Rev. #2: 2	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0 Rev. #2: 0	Rev. #1: 2 Rev. #2: 0	Rev. #2: 0	40
Bakanay, 2005[15]	Rev. #1: 2 Rev. #2: 1	Rev. #1: 1 Rev. #2: 0	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	50
Berthaut, 2008[16]	Rev.: 1	Rev.: 1	Rev.: 1	Rev.: 1			Rev.: 2		33
Chaine, 2001 [17]	Rev. #1: 2 Rev. #2: 0	Rev. #1: 1 Rev. #2: 0	Rev. #1: 2 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #2: 1	Rev. #1: 2 Rev. #2: 2		52
Charache. 1992[18]	Rev. #1: 0 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2		Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	89
Cummins, 2003[19]	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 0	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0 Rev. #2: 0	Rev. #1: 2 Rev. #2: 2	Rev. #2: 0	37
Dahoui, 2010[20]	Rev.: 2	Rev.: 0	Rev.: 1	Rev.: 2	Rev.: 0	Rev.: 0	Rev.: 2	Rev.: 0	44
de Montalembert, 1997[21]	Rev. #1: 0 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 1		Rev. #1: 2 Rev. #2: 2	Rev. #1: 2	85
de Montalembert, 2006[23]	Rev.: 2	Rev.: 1	Rev.: 1	Rev.: 2	Rev.: 1		Rev.: 2	Rev.: 1	71
el-Hazmi, 1992[24]	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 0	Rev. #1: 2 Rev. #2: 2	Rev. #2: 0	57
Ferguson, 2002[25]	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 0 Rev. #2: 1	Rev. #1: 1 Rev. #2: 0	Rev. #1: 2 Rev. #2: 2	Rev. #2: 0	57
Ferster, 2001[26]	Rev. #1: 2 Rev. #2: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2	Rev. #1: 2 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 0 Rev. #2: 2	63
Flanagan, 2010[27]	Rev.: 1	Rev.: 1	Rev.: 2	Rev.: 1			Rev.: 2		39
Gordeuk, 2009[28]	Rev.: 1	Rev.: 0	Rev.: 1	Rev.: 0	Rev.: 0	Rev.: 2	Rev.: 2	Rev.: 0	38
Gulbis, 2005[29]	Rev. #1: 1 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 0 Rev. #2: 1	Rev. #2: 0	Rev. #1: 2 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	54

Table 7. Quality of Observational Studies on Hydroxyurea Use in Sickle Cell Disease* (continued)

Author, year	Study description	Inclusion or exclusion criteria described	Key characteristics of participants described	Intervention described	Adherence to the drug described	Adjusted or stratified estimate of the treatment effect provided	Reported ≥1 objective outcomes	Reported # participants lost to follow-up	Q score
Hanft, 2000[30]	Rev. #1: 1 Rev. #2: 0	Rev. #1: 0 Rev. #2: 0	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 0	Rev. #1: 0 Rev. #2: 0	Rev. #1: 1 Rev. #2: 0	Rev. #1: 2 Rev. #2: 2	Rev. #2: 0	31
Hankins, 2005[31]	Rev. #1: 1 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 0 Rev. #2: 0	Rev. #2: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	67
Hankins, 2007[32]	Rev. #1: 0 Rev. #2: 2	Rev. #1: 1 Rev. #2: 0	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 2	Rev. #1: 0 Rev. #2: 0		Rev. #1: 2 Rev. #2: 2	Rev. #1: 0 Rev. #2: 0	43
Hankins, 2008[33]	Rev.: 1	Rev.: 2	Rev.: 2	Rev.: 1		Rev.: 2	Rev.: 2		63
Harrod, 2007[34]	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0 Rev. #2: 0	Rev. #1: 1 Rev. #2: 0	Rev. #1: 2 Rev. #2: 2		39
Helton, 2009[35]	Rev.: 2	Rev.: 1	Rev.: 1	Rev.: 1	Rev.: 0	Rev.: 2	Rev.: 2	Rev.: N/A	64
Italia, 2009[2]	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 0	Rev.: 2	Rev.: 0	75
Khayat, 2006[36]	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 1 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0		Rev. #1: 2 Rev. #2: 2	Rev. #2: 0	27
Kinney, 1999[37]	Rev. #1: 1 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2		Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	86
Kratovil, 2006[38]	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #2: 1	73
Lefevre, 2008[39]	Rev.: 1	Rev.: 1	Rev.: 1	Rev.: 1			Rev.: 2		33
Little, 2006[40]	Rev.: 2	Rev.: 1	Rev.: 2	Rev.: 2	Rev.: 1	Rev.: 0	Rev.: 2	Rev.: 2	75
Loukopoulos, 1998[41]	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0 Rev. #2: 1	Rev. #1: 0 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0	Rev. #1: 1 Rev. #2: 2	Rev. #1: 0 Rev. #2: 0	23
Loukopoulos, 2000[1]	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2	Rev. #1: 2 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	63
Lukusa, 2009[42]	Rev.: 2	Rev.: 0	Rev.: 1	Rev.: 2	Rev.: 0	Rev.: 0	Rev.: 2	Rev.: 1	50
Maier-Redelsperger, 1998[43]	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 0 Rev. #2: 0	Rev. #1: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	77
Marsenic, 2008[44]	Rev.: 1	Rev.: 2	Rev.: 2	Rev.: 2			Rev.: 1		44
McKie, 2007[45]	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 0	50

Table 7. Quality of Observational Studies on Hydroxyurea Use in Sickle Cell Disease* (continued)

Author, year	Study description	Inclusion or exclusion criteria described	Key characteristics of participants described	Intervention described	Adherence to the drug described	Adjusted or stratified estimate of the treatment effect provided	Reported ≥1 objective outcomes	Reported # participants lost to follow-up	Q score
Odievre, 2008[46]	Rev.: 2	Rev.: 1	Rev.: 1	Rev.: 1			Rev.: 2		39
Olivieri, 1998[47]	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2		Rev. #1: 2 Rev. #2: 2		88
Pashankar, 2008[48]	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 1	Rev.: 0	Rev.: 2	Rev.: 2	81
Puffer, 2007[49]	Rev.: 2	Rev.: 2	Rev.: 2		Rev.: 0	Rev.: 0	Rev.: 2		44
Rigano, 2001[50]	Rev. #1: 1 Rev. #2: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2	Rev. #1: 0 Rev. #2: 2	Rev. #1: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	70
Santos, 2002[51]	Rev. #1: 1 Rev. #2: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0 Rev. #2: 0	Rev. #1: 1 Rev. #2: 2		47
Scott, 1996[53]	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2		Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	93
Singh, 2010[54]	Rev.: 1	Rev.: 1	Rev.: 0	Rev.: 1			Rev.: 2	Rev.: 1	33
Svarch, 2006[55]	Rev. #1: 0 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 1 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0		Rev. #1: 2 Rev. #2: 1	Rev. #2: 0	35
Thornburg, 2009[56]	Rev.: 2	Rev.: 1	Rev.: 2	Rev.: 2	Rev.: 1	Rev.: 0	Rev.: 2	Rev.: 2	75
Thornburg, 2010[57]	Rev.: 2	Rev.: 1	Rev.: 1	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 2	Rev.: 0	75
Vicari, 2005[58]	Rev. #1: 0 Rev. #2: 0	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 1	Rev. #1: 0 Rev. #2: 0	Rev. #1: 0 Rev. #2: 0		Rev. #1: 1 Rev. #2:	Rev. #1: 0 Rev. #2: 0	25
Voskaridou, 1995[59]	Rev. #1: 0 Rev. #2: 1	Rev. #1: 1 Rev. #2: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 0 Rev. #2: 1		Rev. #1: 2 Rev. #2: 2	Rev. #1: 0 Rev. #2: 0	54
Voskaridou, 2010[60]	Rev.: 2	Rev.: 2	Rev.: 1	Rev.: 2	Rev.: 1	Rev.: 0	Rev.: 2	Rev.: 0	63
Wang, 2001[61]	Rev. #1: 1 Rev. #2: 1	Rev. #1: 1 Rev. #2: 2	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 0 Rev. #2: 0	Rev. #2: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	67
Ware, 2002[62]	Rev. #1: 1 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 1 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2		Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 1	86
Ware, 2004[63]	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 1	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2		Rev. #1: 2 Rev. #2: 2		88

Table 7. Quality of Observational Studies on Hydroxyurea Use in Sickle Cell Disease* (continued)

Author, year	Study description	Inclusion or exclusion criteria described	Key characteristics of participants described	Intervention described	Adherence to the drug described	Adjusted or stratified estimate of the treatment effect provided	Reported ≥1 objective outcomes	Reported # participants lost to follow-up	Q score
Zimmerman, 2004[64]	Rev. #1: 2 Rev. #2: 1 Rev. #3: 2	Rev. #1: 1 Rev. #2: 2 Rev. #3: 1	Rev. #1: 2 Rev. #2: 2 Rev. #3: 1	Rev. #1: 2 Rev. #2: 2 Rev. #3: 1	Rev. #1: 1 Rev. #2: 2 Rev. #3: 2		Rev. #2: 2 Rev. #3: 2	Rev. #2: 2 Rev. #3: 1	86
Zimmerman, 2007[65]	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 2	Rev. #1: 2 Rev. #2: 1	Rev. #1: 0 Rev. #2: 1	Rev. #1: 0	Rev. #1: 2 Rev. #2: 2	Rev. #1: 0 Rev. #2: 2	73

* Study quality was assessed by either summing the ratings of two independent reviewers (in that case, quality will be reported in two rows) or by one reviewer, after high agreement of kappa > 0.90 have been established between two independent reviewers (in that case, quality will be reported in one row). Blank cells indicate "not applicable" response by one reviewer. Median age reported instead of mean. Q = quality; Rev. = reviewer.

Quality of included studies was calculated by adding up the scores the study received per question if applicable. Then the result is divided by the maximum score a similar study could obtain and the percentage is used to reflect the quality of the included study. A study received 2 points for a "yes" answer, 1 point for a "to some extent/unclear" answer and no points for a "no" answer. If a question was inapplicable to current study, the answer was left blank and the question was excluded from quality measurement.

The questions used were:

1. Did the study describe the setting or population from which the study sample was drawn?
2. Were the inclusion or exclusion criteria described? (just saying "sickle cell disease" is insufficient)
3. Does the study describe the key characteristics of study participants at enrollment/baseline?
4. Was the intervention described? (intervention may be a drug or an intervention to overcome a barrier)
5. Was there a description of adherence to the drug or the completeness of the intervention?
6. Do the authors report an adjusted or stratified estimate of the treatment effect if this study compared two or more groups?
7. Do the authors report at least one objective outcome from the intervention?
8. Did the study report the number of participants lost to follow-up?

Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease

Author, year	Comparison group (N)	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Acharya, 2009[66]	HU (4) HSMT (6)	NR	NR	Median: 32 [18-34]	100	NR	NR
Al-Jam'a, 2002[13]	NR/NA (27)	NR	NR	21.3 [10-36]	67	NR	Yearly pain crises 6.5 (2.8); Days in hospital 34 (26)
Ataga, 2006[14]	HU with PHTN (9) HU without PHTN (32)	SS 74: SC 12; Sß0 thal 5; Sß+thal 9 (PHTN & no PHTN groups combined)	NR	HU with PHTN: 42.3 (11) HU without PHTN: 38.4 (12)	HU with PHTN: 42 HU without PHTN: 38	NR	HU with PHTN: History of acute chest syndrome, 88%; Crises in past year, 3.0 (3.6); History of stroke, 15% HU without PHTN: History of acute chest syndrome, 82%; Crises in past year: 3.8 (4.3); History of stroke, 8%
Bakanay, 2005[15]	NR/NA (226)	NR	NR	NR	51	NR	
Berthaut, 2008[16]	Before HU (34) During HU (5) After HU (8)	HbSS n = 41, HbSC n = 1, HbS-beta-zero thalassemia n = 2	NR	25.8 [16-48]	100%	NR	
Chaine, 2001[17]	NR/NA (17)	SS 94; Sßo thal 6	Benin 12.5; Senegal 2; CAR 3	27.1 [19-51]	53	Black (100)	2 with leg ulcers
Charache. 1992[18]	NR/NA (49)	SS 100	Benin 61; Senegal, 9.3; CAR 25	27.6	55	Black (100)	
Cummins, 2003[19]	HU (15) CBT(21)	HU: SS 93 CBT: SS 57; SC 29	NR	HU: 33 CBT: 30.9	HU: 67 CBT: 33	NR	
Dahoui, 2010[20]	Normal tricuspid regurgitant velocity (TRV) (58) PHTN (27)	TRV: • HbSS: 70.7 • HbSßo : 5.2 • HbSß+ : 24.1 PHTN: • HbSS: 77.8 • HbSßo : 3.7 • HbSß+ : 18.5	NR	12.9 (7) [2-30]	TRV: 53.5 PHTN: 55.6	Middle Eastern	

Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group (N)	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
de Montalembert, 1997[21]	NR/NA (35)	SS 94; Sß0 thal 3; Sß+thal 3	NR	11* [3-20]	74	NR	Hospital days 29 [0-117]
de Montalembert, 1999[22]	NR/NA (101)	SS 98; Sß+ thal 1; Sß0 thal 1	NR	9.8 [2-20]	55	NR	One HIV+
de Montalembert, 2006[23]	NR/NA (225)	SS 94; SC 1.3; Sßthal 3.5; Hb-Punjab 0.8	NR	9.2 [1.42-19]	61	NR	
el-Hazmi, 1992[24]	NR/NA (21)	SS 71; Sß0 thal 28	NR	[17-32]	NR	NR	
Ferguson, 2002[25]	HU ≥ 24 months (30) HU < 24 months (30)	HU ≥ 24 months: SS 100 HU < 24 months: NR	NR	HU ≥ 24 months: [20-58] HU < 24 months: [19-54]	HU ≥ 24 months:43 HU < 24 months: 30	NR	HU ≥ 24 months:Transfusions 5/yr; Hospitalizations 3.3/year HU < 24 months: Transfusions 5.8/yr; Hospitalizations, 5.7/yr
Ferster, 2001[26]	NR/NA (93)	SS 99; HB-Punjab 1	NR	7* [0.7 to 45]	52	Black (94)	67 had ≥2 pain crises; 9 had stroke; 19 had prior ACS
Flanagan, 2010[27]	HU (37)	NR	NR	NR	NR	NR	
Gordeuk, 2009[28]	HU (150)	HbSS, HbSß, $HbSD^{LA}$: ~75	NR	13 [12-14]	55	NR	
Gulbis, 2005[29]	NR/NA (109)	SS 93; SC 3; Sßo thal 3	NR	6 [.75 - 19]	NR	NR	99 had ≥ 2 pain crises, 21 had prior ACS, 7 had prior stroke, 1 with prior TIA
Hanft, 2000[30]	Adults with MPD and HU exposure (12) Adults with SCD and short HU exposure (15) Children with SCD and no HU (21) Children with SCD and low HU exposure (17)	NR	NR	Adults with MPD and HU exposure: 62 Adults with SCD and short HU exposure: 29 Children with SCD and no HU: 11 Children with SCD and low HU exposure: 11	NR	NR	

Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group (N)	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Hankins, 2005[31]	NR/NA (21)	SS 95; Sß0 thal 5	NR	3.4* [2.6-4.4]	43	Black (100)	
Hankins, 2007[32]	NR/NA (52)	SS 99; Sß0 thal 1	NR	9.9* [3-17.6]	65	Black (98)	
Hankins, 2008[33]	HU (52)	HbSS or Hb SB-thalassemia	NR	Spleen function (median = 10) Brain function (median = 11)	65%	52 Black (98%), 1 White Hispanic (2%)	
Harrod, 2007[34]	HU, no splenectomy (46) No HU, no splenectomy (58) HU with splenectomy (11) No HU with splenectomy (10)	HU, no splenectomy: SS 100 No HU, no Splenectomy: NR HU with Splenectomy: NR No HU with Splenectomy: NR	NR	HU, no splenectomy: 12.1 No HU, no Splenectomy: 4.6 HU with Splenectomy: 10.7 No HU with Splenectomy: 8.7	NR	NR	
Helton, 2009[35]	HU (21)	HbSS	NR	12 [5-17]	71	African-American	Patients had a median of 1 (0–15) painful event within 2 years before MRI examination and a median of 2 (0–4) lifetime ACS episodes

Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group (N)	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Italia, 2009[2]	Adult HbSS (29) Children HbSS (25) Adult Hb Sßthal (23)	Adult HbSS Children HbSS Adult Hb Sßthal	Adult and Children HbSS: 104/108 sickle chromosomes of groups 1, 2 were linked to the Arab-Indian haplotype: (+++−++++−). 3/108 were linked to an atypical haplotype(−−++−+++−) and 1 to another atypical haplotype(+−−−++++−) Adult Hb Sßthal: All sickle chromosomes were linked to the Arab-Indian haplotype except 1 linked with: (+−−−−−++−)	Adult HbSS: [18-35] Children HbSS: [5-17] Adult Hb Sßthal: [18-35]	62	South-Asian	Adult HbSS: • Vaso-occlusive crises > 5/yr: 100% Hospitalizations 1-2/yr : 52% • Hospitalizations 3-4/yr: 17% • Hx of acute chest syn.: 10% • Blood transfusions 1-2/yr: 62% • Blood transfusions 3-5/yr: 10% • Blood transfusions >5/yr: 3% Children HbSS: • Vaso-occlusive crises > 5/yr: 100% Hospitalizations 1-2/yr: 32% • Hospitalizations 3-4/yr: 56% • Hx of acute chest syn.: 8% • Blood transfusions 1-2/yr: 64% • Blood transfusions 3-5/yr:16% Adult Hb Sßthal • Vaso-occlusive crises > 5/yr: 100% Hospitalizations 1-2/yr : 43% • Hospitalizations 3-4/yr: 30% • Hx of acute chest syn.: 0% • Blood transfusions1-2/yr: 35% • Blood transfusions3-5/yr: 35%
Khayat, 2006 [36]	NR/NA (8)	NR	NR	[7-20]	NR	NR	
Kinney, 1999 [37]	NR/NA (84)	SS 100	NR	9.8; 9.1* [5-15]	NR	Black (100)	

Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group (N)	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Kratovil, 2006 [38]	HU (24) No HU (24)	HU: SS 100 No HU: NR	NR	HU: 9.9 [1.7-16] No HU: 9.4 [2.1-16]	HU: 58 No HU: 67	NR	HU: Average of Max TCD velocity 125 (32.3) cm/sec2 No HU: Average of Max TCD velocity, 128.9 cm/sec2 range 79-220
Lefevre, 2008 [39]	HU (80) No HU (39)	NR	NR	NR	NR	NR	HU: 2 strokes
Little, 2006[40]	HU + EPO (13)	HbSS: 92 HbSC: 8	NR	Median: 51 [24-60]	54	NR	NR
Loukopoulos, 1998 [41]	NR/NA (44)	Sß+ thal 34; Sß0 thal 65	NR	NR	NR	NR	
Loukopoulos, 2000 [1]	NR/NA (69)	SS 20; Sß0 thal 79	All HbS was Benin	[17-50]	58	White (100)	
Lukusa, 2009 [42]	HU (4) HSMT(6)	NR	NR	Median: 32 [18-34]	100	NR	NR
Maier-Redelsperger, 1998[43]	NR/NA (29)	NR	Benin 9; Senegal 3; CAR 8	10.9 [4-19]	72	NR	
Marsenic, 2008 [44]	On HU (10) Non HU (22)	On HU: HbSS		On HU: 11.6 Non HU: 8.7	On HU: 40% Non HU: 50%		

Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group (N)	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
McKie, 2007 [45]	HU no microalbuminuria (19) HU and microalbuminuria (9) ACE-Inhibitor for microalbuminuria (9) Usual care (154)	HU no microalbuminuria: SS 100 HU and microalbuminuria: NR ACE-Inhibitor for microalbuminuria: NR Usual care: NR	NR	NR	NR	NR	
Odievre, 2008 [46]	On HU and had vaso-occlusive events (26) Non HU and had vaso-occlusive events (20) Never had vaso-occlusive events (28) Non SCD (controls) (27)	On HU and had vaso-occlusive events: HbSS Non HU and had vaso-occlusive events: HbSS Never had vaso-occlusive events: HbSS Non SCD: • HbAS n = 21 • HbAA n = 6	NR	On HU and had vaso-occlusive events: Median = 10; [4.0-19.0] Non HU and had vaso-occlusive events: Median = 9.5; [6.0-17.0] Never had vaso-occlusive events: Median = 10.5; [5.0-20.0] Non SCD: • HbAS: median = 41 [7.0-66.0] • HbAA: median = 17 [10.0-36.0]			
Olivieri, 1998 [47]	NR/NA (17)	NR	NR	12.4 [5 - 18]	NR	NR	Transfusions, 1.8; (0.5)/yr; Chest syndrome, 1.3; (0.5)/yr; Hospitalized days 29.1; (4.8)/yr

Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group (N)	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Pashankar, 2008 [48]	HU (11) Non HU (8)	HBSS: 100	NR	HU: 13.1 Non HU: 13.3	47.4	NR	NR
Puffer, 2007 [49]	HU (15) No HU (50)	HU: HbSS n = 14, HbS-beta-plus thalassemia n = 1, No HU: HbSS n = 37, HbSC n = 8, HbS-beta-plus thalassemia n = 4, HbS-beta-zero thalassemia n = 1	NR	HU: 14.88 (5.04) No HU: 11.55 (3.03)	NR	NR	
Rigano, 2001 [50]	NR/NA (22)	Sß0 thal 76; Sß+thal 27	Benin 100%	[29-53]	68	White (100)	Pain crises 7/yr (mean)
Santos, 2002 [51]	HU (21)	SS 14; Sß0 thalassemia 7	NR	Mean, 11.7 [3-22]	14	NR	
Schultz, 2003[52]	Patients with cancer (49) Patients on HU who developed cancer (3)	Patients with cancer: SS 63; SC 22; Sß thal 14 Patients on HU who developed cancer: NR	NR	Patients with cancer: 34* [1.2-62]	NR	NR	
Scott, 1996 [53]	NR/NA (15)	SS 73; Sß0 thal 13; Sα+thal 13	NR	14 [(10-17)	40	NR	
Singh, 2010 [54]	HU (24)	NR	NR	NR	NR	NR	
Svarch, 2006 [55]	NR/NA (51)	SS 100	NR	[4-18]	NR	NR	Pain crises 3 [0-4]; Transfusions 3.9 [0-8] Chest syndrome [0-3]; Hospitalizations admissions 4 [0-6]

Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group (N)	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Thornburg, 2009 [56]	HU (14)	HbSS: 100	NR	2.9 [1.75-4.4]	100	NR	12/14 subjects had significant acute clinical events, including dactylitis, painful VOE, bacteremia, ACS and acute anemia: • 2 underwent splenectomy for acute splenic sequestration before enrollment • 2 with subacute splenic sequestration did not undergo splenectomy • 1 developed acute splenic sequestration immediately prior to enrollment • 2 experienced only fever before enrollment
Thornburg, 2010 [57]	HU (75)	HbSS (100)	NR	11.2 [3.5-17.8]	53	African/ AA (74) American Indian (1)	NR
Vicari, 2005 [58]	NR/NA (22)	SS 100	homo Bantu 41; homo Benin 18; hetero Bantu-Benin 31	25.6 [18-46]	32	NR	
Voskaridou, 1995 [59]	NR/NA (14)	Sß+ thal 42; Sß0 thal 58	NR	28.6 [19-48]	64	NR	
Voskaridou, 2010[60]	HU (131) No HU (199)	SS: 10.3; Sß0-thal: 36.7; Sß+-thal: 50	NR	42 [20-76]	41.2	NR	Pain crises: 7.34 (6.5) Hospitalizations: 2.11 (2.96) Transfusions required: 1.53 (5.92)
Wang, 2001[61]	NR/NA (28)	SS 96; Sß0 thal 4	NR	1.3* [0.5-2.3]	57	NR	
Ware, 2002[62]	NR/NA (68)	NR	NR	9.5		NR	
Ware, 2004[63]	NR/NA (35)	SS 94; Sß0 thal 3; S/O Arab 3	NR	11.9 [3 - 19.9]	66	NR	Stroke incidence, 5.7 per 100 patient years

Table 8. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group (N)	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
Zimmerman, 2004[64]	NR/NA (122)	SS 86; SC 5.7 Sß0 thal 5.7; S/O-Arab 1.6	NR	11.1* [0.5 - 19.7]	58	NR	
Zimmerman, 2007[65]	Increased TCD velocities (37)	NR	NR	6.8; 5.6*	NR	NR	Median RMCA, 162 cm/sec2; Median LMCA, 166 cm/sec2

ACE = Angiotensin-Converting Enzyme; ACS = Acute chest syndrome; CAR = Central African Republic; CBT = cognitive behavioral therapy; Hb = hemoglobin; hetero = heterozygous; homo = homozygous; HU = hydroxyurea; HUG-KIDS = Safety of Hydroxyurea in Children With Sickle Cell Anemia; HUSOFT = Hydroxyurea Safety and Organ Toxicity; LMCA = left main coronary artery; MPD = myeloproliferative disorders; NA = not applicable; NR = not reported; PHTN = pulmonary hypertension; RMCA = right middle cerebral artery; Sß+ thal = Sickle ß+ thalassemia; Sß° thal = Sickle ß° thalassemia; S/O-Arab = hemoglobin SO-Arab; Sα+ thal = Sickle α+ thalassemia; SC = Sickle-Hemoglobin C Disease; SCD = Sickle Cell Disease; SD = standard deviation; SS = Sickle Hemoglobin SS Disease; TCD = transcranial Doppler; TIA = transient ischemic attack ; HSMT: hematopoietic stem cell transplantation; EPO = erythropoietin.

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Al-Jam'a, 2002[13]	Adults-Children, prospective	Post-HU (27) Pre-HU	Post-HU: 25.7 (7.3) Median = 25# Pre-HU: 12.6 (5.4)		Post-HU: 10.7 (1.4) median = 10.8# Pre-HU: 9.71 (1.2)		Post-HU: 6,260 (2,580) median 5,600# Pre-HU: 8,990 (3,480)	Pre-HU: 6.5/yr (2.8)	Post-HU: 0.93 (2.2) Median = 0†; Hospital days 5.1 (13.5) median 0# Pre-HU: Hospital days 33.9 (26.1)	
Ataga, 2006[14]	Adults-prospective	HU with PHTN (9) HU without PHTN (32)								In patients with PHTN, 9/26 (35%) were on HU. In patients without PHTN, 32/50 (65%) were on HU
Bakanay, 2005[15]	Children-retrospective	HU (226)								Very little description of study population and treatment, also had concern about confounding by indication.

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Berthaut, 2008[16]	Adult Males, retrospective	Before HU (34) During HU (5) After HU (8)								Before HU: Volume of ejaculate 3.08±1.67 ml, Spermatozoa concentration 38.55±43.12 millions/mL, Total sperm count 114.17±124.12 millions, Initial forward motility 28.66±18.38 % of motile, Spermatozoa morphology 21.92±14.63 % of normal, Vitality 59.75±21.61 % of living During HU: Volume of ejaculate 2.68±1.28 ml, Spermatozoa concentration 2.66±3.75 millions/mL, Total sperm count 7.02±10.18 millions, Initial forward motility 30.00±5.77 % of motile, Spermatozoa morphology 34.50±21.92 % of normal, Vitality 52.00±14.23 % of living After HU: Volume of ejaculate 2.99±2.85 ml, Spermatozoa concentration 18.46 ± 26.86 millions/mL, Total sperm count 61.12±107.37 millions, Initial forward motility 29.46±20.13 % of motile, Spermatozoa morphology 19.16±16.3 % of normal, Vitality 44.40±20.12 % of living
Charache, 1992[18]	Adults-prospective	Post-HU (at MTD) (32 completed) Pre-HU (49)	Post-HU (at MTD): 15 (6) † Pre-HU: 4 (2)	Post-HU (at MTD): 73 (17) † Pre-HU: 28 (14)	Post-HU (at MTD): 9.7 (1.8) † Pre-HU: 8.4 (1.4)	Post-HU (at MTD): 117 (15) † Pre-HU: 94 (8)	Post-HU (at MTD): 8400 (1400) † Pre-HU: 13,400 (3200)	Post-HU (at MTD): 1.3 (2) / 6-months [0 -9]‖ Pre-HU: 4 [020]/6 months		Post-HU (at MTD): Mean 4.3 kg weight gain†

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Cummins, 2003[19]	Adults-prospective with comparison group	HU (15) CBT (21)						HU: 1.4 /yr (2.1) # CBT: 4.3/yr (4.3)	HU: 1.1/yr (2.4) CBT: 0.9/yr (1.2)	Significant improvement in General Health perception (SF36) over CBT group
Dahoui, 2010[20]	Children, adults-cross-sectional	Normal tricuspid regurgitant velocity (58) Pulmonary HTN (27)								Pts on HU had a higher prevalence of PHTN and Hu was not able to stop PHTN from developing in 5 pts
de Montalem-bert, 1997[21]	Children-prospective	Post-HU (35) Pre-HU	Post-HU: 13.7 [3.2-27.0] † Pre-HU: 4 [0.85-13.9]		Post-HU: 9 (1.4) p = 0.03 Pre-HU: 8.4 (1.2)					All but two patients had decreased frequency or termination of crises. No clear difference in weight or height velocity.
el-Hazmi, 1992[24]	Adults-prospective	Post-HU (21) Pre-HU	Post-HU: 19.8 (4)† Pre-HU: 11.8 (3.5)		Post-HU: NR †	Post-HU: NR†	Post-HU: 6,629 (2603) † Pre-HU: 14,0667 (6,716)			P-value relative to baseline

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Ferguson, 2002[25]	Adultsretrospective/ effectiveness	HU ≥24 Months (30) Pre-HU HU <24 months (30) Pre-HU							HU ≥24 Months: 2.1/yr p = .04 relative to baseline Pre-HU: 3.1/yr HU <24 months: 4.8/yr p = 0.49 relative to baseline Pre-HU: 5.7/yr	14 patients were treated for 48 months. Between baseline and year 4: admissions decreased from 3.56 to 1.64 /yr, transfusions 8.64 to 3.00/yr.
Ferster, 2001[26]	Children-prospective	Post-HU (93) Pre-HU	Post-HU: 16.7 (10.6)‖ Pre-HU: 7.3		Post-HU: 8.8 (1.2)‖ Pre-HU: 8.2	Post-HU: 94 (11) ‖ Pre-HU: 91 [70118]			Post-HU: 1.06 / pt-yr Pre-HU: 2.76 (2.3) / pt-yr	Acute chest were 3.5/100 pt-yr, with no strokes during study.
Flanagan, 2010[27]	Children, prospective	HU	Baseline Median = 5.9 MTD Median = 19.1		Baseline Median = 8.1 MTD Median = 9.1		Baseline Median = 12.4 MTD Median = 8.5			Red blood cell count (Baseline Median = 2.7 MTD Median = 2.5) Platelet count (Baseline Median = 495 MTD Median = 364) Absolute neutrophil count (Baseline Median = 5989 MTD Median = 3510) Absolute reticulocyte count (Baseline Median = 246 MTD Median = 126)

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Gordeuk, 2009[28]	Children, young adults-cross-sectional	HU (150) Non HU (247)	HU: 13 [11-15], only in 76 subjects Non HU: 9 [7-10], only in 121 subjects		HU: 9.7 [9.4-9.9], in 147 subjects Non HU: 9.1 [8.9-9.3], in 235 subjects	HU: 92 [90-93],146 subjects Non HU: 81 [79-82], 230 subjects	HU: $8.8X10^9$/L [8.2-9.5], 143 subjects Non HU: $10.7X10^9$/L [10.2-11.2], 230 subjects			Study done to assess possible role of HU and HbF in pulmonary HTN. Pts on HU had higher Hb, HbF but no difference in TRV. Higher level of HbF was independently associated with higher TRV.
Gulbis, 2005[29]	Children-prospective	Post-HU (70) Pre-HU (109)	Post-HU: 1.4 g/dl (HbF) Pre-HU: 0.3 g/dl (HbF)		Post-HU: 8.7 [6.813] at 3 years Pre-HU: 8.2 [6.710]	Post-HU: 91[70-118] Pre-HU: 83 [68113]		Post-HU: 2.2 / pt-yr that required hospital-ization	Post-HU: 1.38 / pt-yr Pre-HU: 3.2 (2.7) / pt-yr	There were 426 total patient years of follow-up. Hematological outcomes at 3 years (n = 70) were 1 stroke and 5 transient ischemic attacks (1.3/100 pt-yrs).
Hankins, 2005[31]	Children-prospective	Post-HU (21) Pre-HU	Post-HU: 23.7 (7.4)‡ Pre-HU: 21.8 (7.8)	Post-HU: 82.6 (7.9) ‡ Pre-HU: 80.6 (14.1)	Post-HU: 9.1 (1.4) ‡ Pre-HU: 8.5 (1.2)	Post-HU: 95.1 (10.4) ‡ Pre-HU: 81.7 (8.0)	Post-HU: 10,100 (5,000) ‡ Pre-HU: 12,600 (4,400)	Post-HU: 33.8/ 100 ptyr com-pared to 32.4/ 100 ptyr in CSSCD §		Post-HU: Outcomes are for 17 children after 4 years of therapy.
Hankins, 2007[32]	Children-prospective	HU								6 patients had recovery of splenic function; 24/25 had stable brain MRIs

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Hankins, 2008[33]	Children, retrospective	Spleen function recovered or was preserved (8) Spleen function had no effect from HU (35)	Spleen function recov-ered or pre-served: Before HU = 9.3, During HU = 22.3 Spleen function had no effect from HU: Before HU = 4.0, During HU = 18.2	NR	Spleen function recovered or preserved: Before HU = 9.1, During HU = 11.1 Spleen function had no effect from HU: Before HU = 8.6, During HU = 9.2	Spleen function recov-ered or pre-served: Before HU = 86 During HU = 104 Spleen function had no effect from HU: Before HU = 86 During HU = 107	Spleen function recovered or preserved: Before HU = 13.5 During HU = 8.7 Spleen function had no effect from HU: Before HU = 15.9 During HU = 8.1	NR	NR	Patients whom brain function showed improvement on MRI (n = 24) Patients whom brain function worsened on MRI (n = 1) (patient had a new punctate hemorrhagic area in the right deep frontal white matter) Patients whom brain function was stable on MRA (n = 24) Patients whom brain function showed improvement on MRA (n = 1)
Harrod, 2007[34]	Children-cross sectional	HU, no splenectomy (46) No HU, no splenectomy (58) HU with splenectomy (11) No HU with splenectomy (10)								HU, no splenectomy: Mature reticulocytes with Howell-Jolly bodies: 3533 ± 2665 No HU, no splenectomy: 1263 ± 1193 HU with splenectomy: 4984 ± 2037 No HU with splenectomy: 2101 ± 945

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Helton, 2009[35]	Children Cross-sectional	HU (21)								Authors concluded that hydroxyurea may normalize gray matter cerebral blood flow in children with SCD, but altered perfusion in white matter may persist
Italia, 2009[2]	Children, adults Prospective	Adult HbSS (29) Children HbSS (25) Adults Hb Sßthal (23)	Adult HbSS: 23.1 (5.2) Chil-dren HbSS: 24.4 (6.3) Adults Hb Sßthal: 26.9 (10)	Adult HbSS: 82.7 (8.7) Children HbSS: 84.4 (10.8) Adults Hb Sßthal: 70.3 (18.2)	Adult HbSS: 10.7 (1.5) Children HbSS: 9.4 (1.9) Adults Hb Sßthal: 9.8 (1.7)	Adult HbSS: 95.4 (11.8) Chil-dren HbSS: 94.5 (10.6) Adults Hb Sßthal: 77.2 (12)	Adult HbSS: 8 (2) Children HbSS: 9.1 (3.4) Adults Hb Sßthal: 8.2 (3.3)	Adult HbSS: 0-1/yr: 83% 2-3/yr: 17% Children HbSS: 0-1/yr: 64% 2-3/yr: 36% Adults Hb Sßthal: 0-1/yr: 87% 2-3/yr: 13%	Adult HbSS: None: 97% 1-2/yr: 3% Children HbSS: None: 96% 1-2/yr: 4% Adults Hb Sßthal: None: 100%	
Kinney, 1999[37]	Children-prospective	Post-HU (84) Pre-HU	Post-HU: 17.8 (7.2)† Pre-HU: 7.3	Post-HU: 66.5 (19.6) † Pre-HU: 34.6 (17.8)	Post-HU: 9 (1.4) † Pre-HU: 7.8	Post-HU: 101.3 (10.2) † Pre-HU: 85.9 (6.6)	Post-HU: 9,200 (3200) † Pre-HU: 13,600			Hematological effects were attained by 6 months (even before MTD). There was little difference between 6 and 12 month data. Continued weight gain and linear growth.

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Kratovil, 2006[38]	Children-prospective with a comparison group	HU (24) No HU	HU: 11.79, [3.8 - 25.4]†† relative to un-treated		HU: 8.2 [5.2 10.6] ‡‡ relative to untreated					HU: Mean of maximum TCD = 111.2 cm/sec No HU: Mean of maximum TCD = 124 cm/sec
Lefevre, 2008[39]	Children, retrospective	HU (80) Non HU (39)	NR	NR	NR	NR	NR	NR	NR	HU: 2 presented stroke; 4 patients with a previous history of stroke but only 1 presented a new episode; recurrence rate of stroke was 2.9 for 100 patient-years; incidence of first stroke 0.36 for 100 patient-years Non HU: Velocity increases with age to a max between age 6 to 9
Little, 2006[40]	Adults, retrospective	A: high-risk SCD with HU intolerance (5) B: high-risk SCD with relative renal insufficiency (5) C: Misc (3)	13.5 [3.1-21], up from 5 [1.6-14]	47.5 [24-75], up from 22 [13 -66]	8.5 [6.7-11.5], up from 6.4 [4.7-8.6]					
Loukopoulos, 1998 [41]	Adultsretro-spective	Post-HU (44) Pre-HU	Post-HU: 23.1 (9.2) Pre-HU: 6.7(4.7)		Post-HU: 9.3 Pre-HU: 8.9	Post-HU: 98.1 (15) Pre-HU: 75.7 (11)				

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Loukopoulos, 2000 [1]	Adults-prospective	Hb SS (14) Hb Sß0 thal (35) Hb Sß+ thal (20)	Hb SS: M: 28 (6.5), F: 26.6 (6.7) Hb Sß0 thal: M: 34.2 (12.8), F: 27.9 (14.3) Hb Sß+ thal: M: 25 (6.3), F: 25.2 (6.4)		Hb SS: M: 10.7 (0.8), F: 9.4 (1.5) Hb Sß0 thal: M: 9.8 (1.7), F: 8.8 (0.8) Hb Sß+ thal: M: 9.2 (1.7), F: 9.1 (1.1)	Hb SS: M: 121.5 (17.3), F: 125.4 (8.3) Hb Sß0 thal: M: 100.4 (12.3) F: 100 (9.4) Hb Sß+ thal: M: 90.9 (11.1) F: 88.7 (12.4)				Mean clinical severity score of 81.7 over 12,018 pt-weeks was down from baseline score of 1182 (arbitrary scale). Outcomes measured at maximum HbF concentrations. HbF% difference was very significant (P < 0.001) in all but female HbSS pts. Hemoglobin difference was very significant (P < 0.001) only in male Hb Sß0 thal pts
Maier-Redelsperger, 1998[43]	Children-prospective	Post-HU (29) Pre-HU	Post-HU: 13 (9.4) Pre-HU: 4 [0.85-13.9]	Post-HU: 54.2 (22.1) Pre-HU: 24.4	Post-HU: 9.1 (0.9) Pre-HU: 8.4 (1.2)	Post-HU: 101.8 (15.9) Pre-HU: 84.5				
Marsenic, 2008 [44]	Children, cross-sectional	On HU (10) Non HU (22)			On HU: 9.13 Non HU: 8.5					On HU: 60% had no proteinuria. Non HU: 42% had no proteinuria.

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
McKie, 2007[45]	Children, prospective	HU with no micro-albuminuria (19) HU + micro-albuminuria (9) HU + micro-albuminurea at baseline (9) Baseline Pre-HU (154)	HU + micro-albumin uria: 19.8 (21.5) n = 7 HU + micro-albumin-urea at base-line: 8.6 (1.0)		HU + micro-albumin-uria: 8.6 (1.0) HU + micro-albumin-urea at baseline: 8.0 (1.4)	HU + micro-albumin-uria: 104.7 (7.1) HU + micro-albumin-urea at base-line: 92.1 (7.0)				HU with no micro-albuminuria: 16/17 remained free from microalbuminuria during treatment HU + micro-albuminuria: 4 of 9 normalized microalbuminuria during treatment
Odievre, 2008[46]	Children, cross-sectional	On HU and had vaso-occlusive events (26) Non HU and had vaso-occlusive events (20) Never had vaso-occlusive events (28) Non SCD (controls) (27)	On Hu: 11.6 Non HU: 6.5 Never had vaso-occlu-sive events: 8.8 Non SCD: 0.2		On HU: 87 Non HU: 79 Never had vaso-occlusive events: 80 Non SCD: 129	On HU: 87.6 Non HU: 84.2 Never had vaso-occlu-sive events: 78.7 Non SCD: 82.1				On HU: PMN+++ 2.3, Platelets 246, Red blood cells 4.7, Reticulocytes 50.85, Hematocrit 39.9 Non HU: PMN 5.7, Platelets 478, Red blood cells 3.1, Reticulocytes 231.68, Hematocrit 4.7 Never had vaso-occlusive events: PMN 5.5, Platelets 434, Red blood cells 2.9, Reticulocytes 303.45, Hematocrit 24.3 Non SCD: PMN 4, Platelets 431, Red blood cells 2.8, Reticulocytes 227.98, Hematocrit 26.6

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Olivieri, 1998[47]	Children-prospective	Post-HU (17) Pre-HU	Post-HU: 16.7 (1.8) Pre-HU: 7.6 (1.6)		Post-HU: 10.2 (3.6) Pre-HU: 8.9 (4.3)	Post-HU: 104 (3) Pre-HU: 87 (7)		Post-HU: 1.2/yr (0.4) Pre-HU: 3.1/yr (0.5)	Post-HU: 1.7/yr (2.0) Pre-HU: 6.7/yr (2.8)	Acute chest syndrome rate declined from 1.3/yr to 0.2/yr. No difference in number of pitted red blood cells (n = 12 children) was observed.
Pashankar, 2008[48]	Children-prospective	HU (6) Non HU (4)			HU: 7.98					TRV and RVP decreased (40.16 to 23.6 mmHg) after 9-12 months of tx. O2 sat increased from 90 to 93%
Puffer, 2007[49]	Children, cross-sectional	HU (15) No HU (50)							HU: Mean 7.40 within 12 months No HU: Mean 3.18 within 12 months	The hydroxyurea group showed higher mean scores on all of the cognitive measures relative to the comparison group though the differences were not all statistically significant. Given that the hydroxyurea group was typically older and had lower household incomes, one might expect their observed scores to be somewhat lower than the comparison group
Rigano, 2001[50]	Adults-prospective	Post-HU (22) Pre-HU	Post-HU: 25.2 (5.2)‡ Pre-HU: 7.5 (5.3)		Post-HU: 10 (1.5) Pre-HU: 6 (1.3)	Post-HU: 96.4 (7.2)‡ Pre-HU: 73.9	Post-HU: 10,200 (3,900) Pre-HU: 11,400 (3900)	Post-HU: 1.1 (1.8)/yr median = 0.5‡ Pre-HU: 7/yr median = 9 (all crises including pain)	Post-HU: 0.5 (1.6)†; hospital days 1.2 (2.3) † Pre-HU: Hospital days 22.4	
Santos, 2002[51]	Children-prospective	HU (21)	15.1§§							10 patients had improvement in splenic function

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Scott, 1996[53]	Children-prospective	Post-HU (15) Pre-HU	Post-HU: 15.2 (9.8,) [4.1-31] ¶ Pre-HU: 6.9 (6.2)		Post-HU: 9.5 (1.5) [7.7-13.1] Pre-HU: 8.2 (1.0)	Post-HU: 100 (15) [80-127) † Pre-HU: 85 (11)			Post-HU: 3/yr (4) Pre-HU: 7/yr(2.4)	
Singh, 2010[54]	NR, prospective	HU (24)	Before HU 9.15, after 1 year 9.98			Before HU 82.57, after 1 year 89.87				
Svarch, 2006[55]	Children - retrospective	HU (51) Baseline (pre-HU)	HU: 12.4 (7.9) † Base-line: 6.4		HU: 8.5 (1) p = .0001 Baseline: 7.8		HU: 9,800 (2,100) p = 0.12 Baseline: 10,900	HU: Median 0.8/yr [0-2] Baseline: Median 3/yr	HU: 0.5 [04] Baseline: 4 [0-6]	HU: Resource-poor environment
Thornburg, 2009[56]	Children, prospective	HU (14)	25.9 (6.6)		9.5 (1)	99 (12)				
Thornburg, 2010[57]	Children-prospective	HU (75)	8% increase [6.2-9.8]		1.3 [1.0-1.5]					1699 cells/mm3 decrease in absolute neutrophil count
Vicari, 2005[58]	Adults-prospective	Post-HU (22) Pre-HU	Post-HU: 10.2 (5)** Pre-HU: 5 (3)		Post-HU: 8.6(1.1)‡ Pre-HU: 7.9 (0.9)					Post-HU: Outcomes reported by haplotype.

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Voskaridou, 1995[59]	Adults-prospective	Post-HU (14) Pre-HU	Post-HU: 22.9 (7.7) Pre-HU: 3.6 (2.1)		Post-HU: 9 (1.3) Pre-HU: 9.0 (1.2)	Post-HU: 95 (14.1) Pre-HU: 71.9 (5.7)				
Voskaridou, 2010[60]	Adults-prospective	HU (131) Non HU (199)	HU: 17.4 [0.8-38.3] Non HU: 4.9 [0.8-38.3)		HU: 9.5 [6.3-13] Non HU: 9.1 [5.5-13.6]	HU: 96.8 [79.8 127.2] Non HU: 71.1 [62.8-99.2]		HU: 0.025 (0.026) >95% reduction	HU: 0.041 (0.018)	Some outcome data not reported for non HU arm. Some outcomes were reported per year.
Wang, 2001[61]	Children-prospective	Post-HU (28) Pre-HU CSSCD	Post-HU: 20.3 (4.9) Pre-HU: 21.8 (7.8) CSSCD: 10.9 (7.9)	Post-HU: 76.2 (12.4) Pre-HU: 80.6 (14.1) CSSCD: 65.4 (11.2)	Post-HU: 8.8 (1.2) Pre-HU: 8.5 (1.2) CSSCD: 7.7 (1.0)	Post-HU: 90 (9.6) Pre-HU: 81.7 (8.0) CSSCD: 84.1 (10.1)	Post-HU: 10,100 (3,200) Pre-HU: 12600 (4,400) CSSCD: 14,300 (2,400)			Post-HU: Outcomes are for 21 patients who completed 2 years of treatment (not necessarily on MTD).

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Ware, 2002[62]	Children-prospective	Post-HU (68) Pre-HU	Post-HU: Median = 17.6, [2.9-32.4] Pre-HU: 6.7		Pre-HU: 7.7	Pre-HU: 85.7	Pre-HU: 14,000			HbF% was predicted by HbF% at baseline (p = .001) and Hb at baseline (p = 0.01); HbF% was negatively associated with # of pills returned (p = 0.02), postively with change in Hb (p < 0.0001), MCV (p = 0.01) and decline in reticulocytes (p = 0.01), and decline in white blood count (p = 0.006).
Ware, 2004[63]	Children-prospective	HU (35)	18.6 (6.6)		9.2(1.4)	112(9)	7300 (2500)			Data collected on two groups; patients initiating HU after an abrupt halt to transfusion therapy, and patients initiating HU before transfusion therapy was completely halted. Pooled data was presented here. Stroke recurrence rate 5/7/100 pt-yrs (7 children, 4 of whom were noncompliant with HU).
Zimmerman, 2004[64]	Children-prospective	Post-HU (122) Pre-HU	Post-HU: 19.7 (8.5)‡ Pre-HU: 7.6		Post-HU: 9.7 (1.3) ‡ Pre-HU: 8.2	Post-HU: 105.8 (13.8) ‡ Pre-HU: 84.4 (8.5)	Post-HU: 7.0 Pre-HU: 12,400			Efficacy (in Hb, MCV, % Hb F, WBC count, ANC, reticulocyte, bilirubin) maintained over 7 years of follow-up.

Table 9. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm (N)	Hb F%*	%F cells*	Hemoglo-bin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Zimmerman, 2007[65]	Children - prospective	Patients with increased TCD velocities post HU (37) Patients with increased TCD velocities pre HU	Patients with increased TCD velocities post HU: 22.7 (7.9) median = 23.3 † Patients with increased TCD velocities pre HU: 10.3		Patients with increased TCD velocities post HU: 9.4 (1.1) median = 9.4 † Patients with increased TCD velocities pre HU: 7.8	Patients with increased TCD velocities post HU: 104 (9) median † Patients with increased TCD velocities pre HU: 86 (8)				Patients with increased TCD velocities post HU: Significant decline in TCD of RMCA, LMCA, RACA, LACA, and LPCA, but not RPCA. Stroke rate on treatment 0.52/100 ptyears, RMCA on treatment 134 cm/sec, p < .0001. Patients with increased TCD velocities pre HU: RMCA 162 cm/sec

* Mean, (SD) [range] unless otherwise noted # p ≤ 0.005

† p ≤ 0.0001 **p = 0.0002

‡ p ≤ 0.001 ††p ≤ 0.00001 § p ≤ not significant ‡‡ p = 0.057 ‖ p ≤ 0.01 §§ Change from baseline ¶ p ≤ 0.002

ANC = absolute neutrophil count; CBT = cognitive based therapy; CSSCD = Cooperative Study of Sickle Cell Disease; Hb = hemoglobin; HbF = fetal hemoglobin; HTN = hypertension; HU = hydroxyurea; HUG-KIDS = Safety of Hydroxyurea in Children With Sickle Cell Anemia; LACA = left anterior cerebral artery; LMCA = left main coronary artery; LPCA = left posterior cerebral artery; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; NR = not reported; PHTN = pulmonary hypertension; pt-yr = patient-year; RACA = right anterior cerebral artery; RMCA = right middle cerebral artery; RPCA = right posterior cerebral artery; SCD = sickle cell disease; SD = standard deviation; TCD = transcranial Doppler; WBC = white blood cell; TRV: tricuspid regurgitant velocity; RVP: right ventricle pressure

Table 10. Toxicities of Hydroxyurea Observational Studies in Sickle Cell Disease

Author	Group	Primarily toxicity study	Deaths, n (per pt/yr)	Neutropenia	Thrombocytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other
Berthaut, 2008[16]	Before HU (34) During HU (5) After HU (8)								Before HU: Volume of ejaculate 3.08±1.67 ml, Spermatozoa concentration 38.55±43.12 millions/mL, Total sperm count 114.17±124.12 millions, Initial forward motility 28.66±18.38 % of motile, Spermatozoa morphology 21.92±14.63 % of normal, Vitality 59.75±21.61 % of living During HU: Volume of ejaculate 2.68±1.28 ml, Spermatozoa concentration 2.66±3.75 millions/mL, Total sperm count 7.02±10.18 millions, Initial forward motility 30.00±5.77 % of motile, Spermatozoa morphology 34.50±21.92 % of normal, Vitality 52.00±14.23 % of living After HU: Volume of ejaculate 2.99±2.85 ml, Spermatozoa concentration 18.46 ± 26.86 millions/mL, Total sperm count 61.12±107.37 millions, Initial forward motility 29.46±20.13 % of motile, Spermatozoa morphology 19.16±16.3 % of normal, Vitality 44.40±20.12 % of living

Table 10. Toxicities of Hydroxyurea Observational Studies in Sickle Cell Disease (continued)

Author	Group	Primarily toxicity study	Deaths, n (per pt/yr)	Neutropenia	Thrombocytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other
Chaine, 2001[17]	HU (17)	Yes					5	13	Prior leg ulcer associated with ulcer on treatment ($p < .005$); patients with ulcer were older than those without ($p < .001$); 3 of 5 resolved with holding HU
Charache. 1992[18]	HU (49)			17	1				No unusual infections; karotypic analysis showed no difference in % abnormal chromosomes pre and post treatment
de Montalembert, 1997[21]	HU (35)							5	
de Montalembert, 1999 [22]	HU (101)	Yes		2 with ANC 500-1000/µl 3 with ANC 1000-1500/µl	4 with 90100,000/µl	1	1	8	
de Montalembert, 2006[23]	HU (225)	Yes	1	8	8	1 (same patient as in earlier study [67])			81 patients discontinued therapy, mostly for lack of efficacy
el-Hazmi, 1992[24]	HU (21)								6 with leukopenia (WBC < 4500/µl)
Ferguson, 2002[25]	HU ≥ 24 months (30) HU < 24 months (30)								HU ≥ 24 months : Stated no adverse events HU < 24 months
Gulbis, 2005[29]	HU (109)		1 (0.23/ 100)						Transient hematological toxicity in 1.4/100 pt-yrs
Hanft, 2000[30]	HU and no HU (SCD and MPD) (95)	Yes							HPRT cloning efficiency and VDJ recombination events described in text.

Table 10. Toxicities of Hydroxyurea Observational Studies in Sickle Cell Disease (continued)

Author	Group	Primarily toxicity study	Deaths, n (per pt/yr)	Neutropenia	Thrombocytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other
Hankins, 2005[31]	HU (21)		1	21 episodes in 10 patients in year 3, 21 episodes in 9 patients in year 4	2 in year 5, 1 in year 6				Severe anemia 3 times in 3 patients in year 3; 4 times in 1 patient in year 4.
Italia, 2008[2]	HU (77)	No		1					
Khayat, 2006[36]	HU (8)	Yes							There was no significant difference in mitotic index ($p > 0.05$). There was no significant difference in chromosomal aberrations ($p > 0.05$) pre-and post-treatment
Kinney, 1999 [37]	HU (84)	Yes		56 with ANC < 2000/µl	7			5	
Loukopoulos, 2000 [1]	HU (69)						3	0	2 with severe anemia; 0/40 with oncogenes; 0/10 with cytogenetic abnormalities
Olivieri, 1998 [47]	HU (17)	Yes		9	3			1	
Scott, 1996 [53]	HU (15)		1					1	Anemia in 3 of 13 completing study
Schultz, 2003 [52]	Patients with SCD and cancer (49) Patients on HU with cancer (3)	Patients with SCD and cancer: Yes				Patients with SCD and cancer: 7 of 16,613; not all on HU Patients on HU with cancer: 1			Patients with SCD and cancer: 49 cancers in patients with SCD described, in survey of providers Patients on HU with cancer: Unknown # taking HU, but among 49 patients, 3 were on HU, including 1 with leukemia
Thornburg, 2009 [56]	HU (14)	Yes		11	4				2 patients had combined cytopenias

Table 10. Toxicities of Hydroxyurea Observational Studies in Sickle Cell Disease (continued)

Author	Group	Primarily toxicity study	Deaths, n (per pt/yr)	Neutropenia	Thrombocytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other
Thornburg, 2010 [57]	HU (75)	No		Mean change in neutrophil count: –1699 cells/mm3; 95% CI, –2513-–885; P < .0001					
Vicari, 2005[58]	HU (22)			3					
Voskaridou, 1995 [59]	HU (14)								Leukopenia or thrombocytopenia in 6; rapidly reversed by holding therapy
Wang, 2001[61]	HU (28)		1	17 with ANC < 1500/µl 6 with ANC < 500/µl	1 with <80,000/µl				
Zimmerman, 2004[64]	HU (122)		(2/455)			0			No increase in the acquired illegitimate VDJ rearrangements.

ANC = absolute neutrophil count; HPRT = hypoxanthine phosphoribosyl transferase; HU = hydroxyurea; HUG-KID = pediatric hydroxyurea safety trial; HUSOFT = The Hydroxyurea Safety and Organ Toxicity trial; MPD = myeloproliferative disorders; SCD = Sickle Cell Disease; WBC = white blood cells.

Table 11. Toxicities of Hydroxyurea Reported in Multi-Arm Observational Studies in Sickle Cell Disease Published After 2007

Author	Group (N)	Primarily toxicity study	Deaths, n (per pt/yr)	Neutropenia	Thrombocytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other
Little, 2006[40]	A: High-risk SCD with HU intolerance (5) B: High-risk SCD with relative renal insufficiency (5) C: Misc (3)	No							A: high-risk SCD with HU intolerance: 1 patient developed liver failure and renal end-stage renal disease. Following liver transplant and EPO cessation, patient's condition stabilized
Lukusa, 2009 [42]	HU (4) HSCT (6)	Yes							HU: 2 pts were azoospermic HSCT: 3 pts were azoospermic
Voskaridou, 2010[60]	HU (131) Non HU(199)	Yes	HU: 13 Non HU: 49	HU: 9	HU: 8			HU: 1	HU: 2 pts developed red cell aplasia. 2 pts developed alopecia.

TRV: tricuspid regurgitant jet velocity, pt: patient, HU: hydroxyurea, HSCT: hematopoietic stem cell transplantation; EPO: erythropoietin

Table 12. Toxicity Results From Case Reports in Hydroxyurea Treatment of Sickle Cell Disease Only

Outcome	Number of case reports	Females/ Males	Mean age at toxicity	Median # of weeks on HU until toxicity	# of case reports with certain causality	# of reports with probable causality	# of reports with possible causality
Leg ulcer	1	1/0	45	104	0	0	1
Leukemia	3	3/0	32	288	0	0	3
Cytopenia	1	1/0	26	153	0	1	0
Avascular necrosis	3	2/1	19	NR, 104	0	0	3
Splenomegaly	1	1/0	32	NR	0	0	1
Cryptosporidial infection	1	1/0	36	80	0	0	1
Intracranial hemorrhage/thrombosis	2	0/2	21.5	52	0	0	2
Hodgkin's lymphoma	3	0/3	8	26	0	1	2
Low sperm count/ Motility decrease	4	0/4	31	128	0	0	4
Acute myocardial infarction	1	0/1	28	NR	0	0	1
Hyperpigmentation of skin	2	1/1	16	75	0	0	2
mild transient myelotoxicity	1	1/0	4	NR	1	0	
Azoospermia	3	0/3	29	17	0	1	2

[68]: for papers published before July, 2007

[69-73]: July, 2007- present

* WHO causality assessment

HU = hydroxyurea; NR = not reported.

A reaction was rated as “certain” if all four criteria for causality were fulfilled: (1) a plausible time relationship between drug administration and an event; (2) an absence of a concurrent disease that might have caused the event; (3) a reasonable response to drug withdrawal; and (4) existence of a re-challenge or a demonstrated biological explanation. A reaction was rated as "probable" if criteria 1, 2, and 3 were fulfilled and “possible if only criterion 1 was met and information on criterion 3 was lacking or unclear. A reaction was rated as "unlikely" if criterion 1 was not met and if other drugs, chemicals, or underlying disease provided a plausible explanation for the reaction.

1. Is the time relationship from drug administration to the event *plausible* for causality to be established?
2. Is there an absence of concurrent diseases or other drugs that may have caused the event?
3. Is there a reasonable response to drug withdrawal?
4. Is there the existence of a re-challenge in this report or a demonstrated biological/pharmacological explanation?

Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Athanassiou, 2006[74]	Europe	**Inclusion**: Sß° thal, S α+ thal SCD no HU	HU SCD or HU NO SCD or HU		60 months	Index of rigidity (IR)	HU: 31.9± 12.2* SCD or HU: 46.1± 13.08 NO SCD or HU: 13.15± 0.5	Mean elastic shear modulus (u x 10^-3 dyn/cm)	HU: 15± 1.3† SCD or HU: 21.1± 2.1		
Flanagan, 2010[27]	North America	Inclusion: Children with SCD on HU	HU			micronuclei (MN) in red blood cells (RBCs)	exposure to hydroxyurea was associated with significantly increased frequencies of MN-CD71+ and MN-RBC compared to baseline. The increases were evident by 3 months of therapy, and did not escalate further with up to 12 years of continuous drug exposure, also there was no association between MN production and hydroxyurea dose				

Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Gambero, 2007[75]	South America	Inclusion: HbSS or Hb a-thalassaemia, not in crisis, had not received blood transfusions in the preceding 3 months and patients on HU therapy had been taking 20–30 mg/kg/d for at least 3 months.	Sickle cell on HU Sickle cell Non-HU Non Sickle cell	Sickle cell on HU: NR	Sickle cell on HU: NR	Adherence to fibronectin	Red cells from patients on HU therapy have a decreased ability to adhere to fibronectin in comparison with red cells from patients not on HU.	Reticulo-cytes count	slightly lower than that of SS patients not on HU, significantly higher (P < 0.001) than that of normal red cells	Adhesion molecules	HU is more likely to have an indirect effect on sickle red cell adhesion (i.e. mediated by decreased gene expression) rather than a direct effect on the affinity of the adhesion molecules already expressed on the red cell surface.

Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Harrod, 2007[34]	North America	**Inclusion**: pediatric sickle cell patients, HbSS or HbSC, age 0 to 19 years.	HU	NR	NR	Howell-Jolly Bodies	HJB was significantly influenced by hydroxyurea exposure	CD71+ reticulo-cytes	HU exposure in children with HbSS was associated with a significantly lower percentage of CD71+ reticulo-cytes, presumably reflecting the mild marrow suppression		

Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Heeney, 2003[76]	North America	**Inclusion**: Children; SCA; S ß+ thal; S ßo thal **Exclusion**: HU before age 5 years; No labs before HU; <12 months of HU; Unknown or rare UGT1A genotype	UGT1A 6/6 UGT1A 6/7 UGT1A 7/7	UGT1A 6/6: 15-20 mg/kg/day: every 8 weeks to max of 30-35 mg/kg/day UGT1A 6/7: 15-20 mg/kg/day: every 8 weeks to max of 30-35 mg/kg/day UGT1A 7/7: 15-20 mg/kg/day: every 8 weeks to max of 30-35 mg/kg/day	at least 12 months	Hb F (%)‡	UGT1A 6/6: 16.4 UGT1A 6/7: 12.1 UGT1A 7/7: 13.5	Hb (g/dl)‡	UGT1A 6/6: 1.7 UGT1A 6/7: 1.5 UGT1A 7/7: 1.9	Total bilirubin (mg/dl)‡	UGT1A 6/6: -1.4 UGT1A 6/7: -1.3 UGT1A 7/7: -2.8

Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Italia, 2009[2]	USA	**Inclusion:** frequent vaso-occlusive crises (>5/yr), CNS affected at least once in the past, acute chest syndrome > twice in the past, avascular necrosis of femoral head along with any of the above	HU	10 15 mg/kg/day	2 yrs	Xmn I polymorph-ism	50 pts from groups I & II were Xmn I +/+ & 4 were +/−, while 8 pts from group III were Xmn I +/+, 14 were +/− and 1 was −/−. The latter had HbF level of 25.0% before and 28.0% after tx. Pts with Xmn I +/+ had a mean HbF level of 17.0±6% before & 24.0±7% after tx while those with Xmn I +/− had a mean HbF level of 16.0±10% before & 26.0 ±12% after tx	γ mRNA expression	A significant increase in γ gene mRNA levels was seen after therapy which correlated with an increase in HbF levels studied among 10 patients	(AT)x(T)y motif	3 different motifs, (AT) 9(T)5, (AT)8 (T)9 and (AT) 7(T)7 were found in 4 different genotypes.

Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Iyamu, 2005[77]	North America	**Inclusion**: Age 8-21; SCA; in steady state **Exclusion**: Transfusion in last 6 months; smoking; SA	HU steady-state No HU steady-state African American Hb AA	HU steady-state: 15-30 mg/kg/d No HU steady-state: No HU African American Hb AA: No HU	HU steady-state: Cross-sectional	HU steady-state: Hb F %	HU steady-state: 13.8 No HU steady-state: 6.8	HU steady-state: Nitric oxide synthase No HU steady-state: (nmol/ml/min)	HU steady-state: 0.50 No HU steady-state: 0.27 African American Hb AA: 0.32	HU steady-state: Arginase (U/nmol/1 No HU steady-state: 0^8 cells ± SEM)	HU steady-state: 1.36± 0.20‡ No HU steady-state: 3.31± 0.29 African American Hb AA: 0.23
Lapou-meroulie, 2005[78]	Europe	**Inclusion**: Children, SCA in steady-state	Clinical events (8 on HU, 10 untreated) Steady state, No HU Steady state, HU Healthy AA		>12 months	Endothelin - 1 (pg/ml ± SEM)	Clinical events (8 on HU, 10 untreated): 1.32± 0.17 Steady state, No HU: 0.65± 0.11 Steady state, HU: 0.37± 0.05† Healthy AA: 0.65± 0.07				
Maluf, 2009[79]	South America	**Inclusion**: HbSS, on HU at least 6 months	Sickle cell on HU Non Sickle cell			Micro-nucleus frequency	Sickle cell on HU: 4.74 Non Sickle cell: 3.47	Frequency of Nucleo-plasmic bridges / nuclear buds	There was no significant difference between the 2 groups		

Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Nahavandi, 2002[80]	North America	**Inclusion**: SCA **Exclusion**: Transfusion within 3 months; significant renal insufficiency ; infection; PHT	HU Non-HU Steady state HU during VOC Non-HU during VOC	HU: 1200 mg/d Non-HU steady state: No HU HU during VOC: 1200 mg/d Non-HU during VOC: No HU	HU: 35	HU: Hb F% (range)	HU: 17 (6.7-28) Non-HU steady state: 3.6, (1.7-6)§ HU during VOC: 19 (7-31) Non-HU during VOC: 4.2 (1.5-6.7)§	HU: Cyclic GMP (pmol/ml ± SEM)	HU: 2.45± 0.32 Non-HU steady state: 1.75± 0.42 HU during VOC: 2.56± 0.3 Non-HU during VOC: 1.56± 0.1§	HU: Nitric oxide metabolite Non-HU steady state: s (microM ± SEM)	HU: 29± 2.5 Non-HU steady state: 19± 1.8§ HU during VOC: 32± 5 Non-HU during VOC: 17± 1.7§
Nahavandi, 2003[81]	North America	**Inclusion**: Age 18-48; SCA **Exclusion**: ACS; transfused in last three months; renal insufficiency ; infection; hypoxemia	HU, no VOC No HU no VOC HU and VOC No HU, VOC	HU, no VOC: 1000-1500 mg/day HU and VOC: 1000-1500 mg/day		Venous oxyhemo-globin (%)	HU, no VOC: 65 No HU no VOC: 60 HU and VOC: 81 No HU, VOC: 73	Venous reduced Hb (%)	HU, no VOC: 28 No HU no VOC: 36 HU and VOC: 13 No HU, VOC: 22	Nitric Oxide Metabo-lites (µM)	HU, no VOC: 17 ± 9§

Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Odievre, 2008[46]	Europe	**Inclusion:** children, HbSS	On HU and had vaso-occlusive events Non HU and had vaso-occlusive events Never had vaso-occlusive events Non SCD (controls)			Adhesion molecules	Reticulocytes and/or red blood cells from the children with sickle cell disease showed significantly higher expression of CD36,a4b1, Lu/BCAM than those from controls, whatever the severity of the disease, as well as less marked increases in expression of ICAM-4, CD47 and CD147. Under hydroxyurea treatment, the expression of CD36, a4b1 and ICAM-4 (to a lesser extent) was decreased, but surprisingly the expression of Lu/BCAM (and also CD47 and CD147 to a lesser extent) was significantly increased.				

Table 13. Description and Results of Studies (Cohort With Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Tavakkoli, 2004[82]	North America	**Inclusion**: SCA **Exclusion:** Transfusion in last 3 months	HU Steady state condition, not on HU VOC, on HU VOC, not on HU	HU: 1000-1500mg: N/A VOC, on HU: 1000-1500mg: N/A		TNF-α (pm/ml)	HU: 4.89 Steady state condition, not on HU: 3.78 VOC, on HU: 6.45 VOC, not on HU: 5.86				
Teixeira, 2003[83]	South America/ Mexico	**Inclusion**: SCA, S ß+ thal; S ßo thal; S α+ thal; SC; Age >12	HU No HU		2 to 60 months	Hb F (%)	HU: 14.2± 8.3§ No HU: 8.8± 4.1	HU: Hb (g/dl)	HU: 9.6± 2.2§ No HU: 8.1± 0.9		
Ulug, 2008[84]	Europe	**Inclusion**: HbSS	On-HU Off-HU Non-HU	On-HU: 500 mg/day	On-HU: NR	plasma cfDNA levels	On-HU: Mean 804 Off-HU: Mean 2481 Non-HU: Mean 975	HbF increase / MCV increase	On-HU: Mean 16.07 / mean 103.01 Off-HU: Mean 7.08 / mean 84.56 Non-HU: NR	total Hb increase	On-HU: Mean 8.95 Off-HU: Mean 8.00 Non-HU: NR

* p = 0.02

†p = 0.03

‡ p < 0.001§ p < 0.05

AA = African American; ACS = acute chest syndrome; GMP = granual membrane protein; Hb = hemoglobin; HU = hydroxyurea; IR = index of rigidity; N/A = not applicable; PHT = pulmonary hyptertension; S ß+ thal = S ß+ thalassemia; S ßº thal = S ßº thalassemia; S α+ thal = S α+ thalassemia; SA = Substance abuse; SC = Sickle-Hemoglobin C Disease; SCA = sickle cell anemia; SCD = Sickle cell disease; SEM = standard error of the mean; TNF-α = tumor necrosis factor alpha; VOC = vaso-occlusive crisis.

Table 14. Patient Characteristics in Studies Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease

Author, year	Intervention (N)	Age, mean (SD) [range]*	Male, n (%)	Genotype/haplotype (%)	Last observation
Athanassiou, 2006[74]	HU (22)	HU: Median, 30; [20-46]	HU: 14	NR	NR
	SCD no HU (14)	SCD no HU: Median, 32; [25-42]	SCD no HU: 5		
	NO SCD or HU (5)	No SCD or HU: Mean, similar age	No SCD or HU: 40		
Flanagan, 2010[27]	HU (105)	NR	NR	NR	
Gambero, 2007[75]	Sickle cell on HU (14)	Sickle cell on HU: 31.9	Sickle cell on HU: 8	HbSS or Hb a-thalassaemia	NR
	Sickle cell Non-HU (28)	Sickle cell Non-HU: 32			
	Non Sickle cell		Sickle cell Non-HU: 9		
Harrod, 2007[34]	HU (57)	11.8		HbSS	
Heeney, 2003[76]	HU UGT1A 6/6 (17)	HU UGT1A 6/6: Mean, 11.4	HU UGT1A 6/6: 13	NR	At least 12 months
	HU UGT1A 6/7 (24)	HU UGT1A 6/7: Mean, 11.3			
	HU UGT1A 7/7 (18)	HU UGT1A 7/7: Mean, 12.6	HU UGT1A 6/7: 15		
			HU UGT1A 7/7: 11		
Iyamu, 2005[77]	HU, steady state (23)	HU, steady state: 13.5 [9-21]	NR	HU, steady state: SS, (100)	Cross-sectional-once
	No HU, steady state (12)	No HU, steady state: 12.5 [(8-19] 15.6 [11-21]		No HU, steady state: SS, (100)	
	African-American Hb AA (10)			African-American Hb AA: Hb AA (100)	
Lapoumeroul ie, 2005[78]	Clinical events; Hb SS 8 HU, 10 none (18)	Clinical events; Hb SS 8 HU, 10 none: [2.9-13.2]	NR	SS, (100)	NR
	Hb SS, no HU (17)	Hb SS, no HU: [3.0-14.9]			
	Hb SS, HU (16)	Hb SS, HU [3.5-15.1]			
	NI AA, controls none (26)	NI AA, controls none [2.6-15.8]			
Maluf, 2009[79]	Sickle cell on HU (35)	26.3	Sickle cell on HU: 43%	Sickle cell on HU: HbSS	
	Non Sickle cell (34)				

Table 14. Patient Characteristics in Studies Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Intervention (N)	Age, mean (SD) [range]*	Male, n (%)	Genotype/haplotype (%)	Last observation
Nahavandi, 2002[80]	HU (12) Non-HU steady state (26) HU during VOC (14) Non-HU during VOC (12)	HU: 32 [18-47] Non-HU steady state: 34 [18-53] HU during VOC: 34 [18-48] Non-HU during VOC: 31 [18-45]	HU: 9 8 8 NR	SS, (100)	NR
Nahavandi, 2003[81]	HU (12) HU untreated, with VOC (12) HU treated, with VOC (14) HU untreated control,no VOC (31)	HU: 32 [18-47] HU untreated, with VOC: 31 [18-45] HU treated, with VOC: 34 [18-48] HU untreated control,no VOC: 34 [18-53]	HU: 9 HU untreated, with VOC: 8 HU treated, with VOC: 8 HU untreated control,no VOC: NR	SS, (100)	NR
Odievre, 2008[46]	On HU and had vaso-occlusive events (26) Non HU and had vaso-occlusive events (20) Never had vaso-occlusive events (28) Non SCD (controls) (27)	On HU and had vaso-occlusive events: Median = 10; [4.0-19.0] Non HU and had vaso-occlusive events: Median = 9.5; [6.0-17.0] Never had vaso-occlusive events: Median = 10.5; [5.0-20.0] Non SCD: HbAS: median = 41 [7.0-66.0]; HbAA: median = 17 [10.0-36.0]		On HU and had vaso-occlusive events; non HU and had vaso-occlusive events; and never had vaso-occlusive events: HbSS Non SCD: HbAS n = 21, HbAA n = 6	
Tavakkoli, 2004[82]	HU (10) Steady state condition, not on HU VOC, on HU (10) VOC, not on HU (10) No HU (30)	HU: 32 [18-47] VOC, on HU: 34 [15-53] VOC, not on HU: 34 [18-48] No HU: 31 [18-45]	NR	SS, (100)	NR

Table 14. Patient Characteristics in Studies Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Intervention (N)	Age, mean (SD) [range]*	Male, n (%)	Genotype/haplotype (%)	Last observation
Teixeira, 2003[83]	HU (31)	NR	NR	NR	NR
	No HU (30)				
Ulug, 2008[84]	On-HU (10)	On-HU: NR	On-HU: NR	All HbSS	NR
	Off-HU (10)	Off-HU: NR	Off-HU: NR		
	Non-HU (115)	Non-HU: NR	Non-HU: 46		

* Unless otherwise specified.

† Recruitment start and end dates as well as race of patients were unreported for all studies in this table.

AA = African American; Hb = hemoglobin; HU = hydroxyurea; NR = not reported; SCD = sickle cell disease; SD = standard deviation; SS = Sickle Hemoglobin SS Disease; VOC = vaso-occlusive crisis

Table 15. Adequacy of Reporting in Biomarker Studies in Sickle Cell Disease

Author, year	Source population	Inclusion criteria	Baseline characteristics	Intervention	Adherence	Adjustment when reporting outcome comparisons	Objective outcome	Losses to follow-up	Quality score
Athanassiou, 2006[74]	0.5	0.5	1	0	0	0	2		29
Gambero, 2007[75]	1	1	1	1			2		33
Harrod, 2007[34]	1	2	1				2		33
Heeney, 2003[76]	1	2	1.5	2	0	0	2		57
Iyamu, 2005[77]	0	0.5	1	1	0	0	2		32
Lapoumeroulie, 2005[78]	1	0	1	0	0		2		29
Maluf, 2009[79]	1	1	1				2		28
Nahavandi, 2002[80]	0.5	1	1	1	0	0	2		39
Nahavandi, 2003 [81]	1.5	1.5	2	1	0	0	2	0	50
Odievre, 2008[46]	2	1	1	1			2		39
Tavakkoli, 2004[82]	1	1	1.5	1.5		0	2		58
Teixeira, 2003[83]	1	0	0.5	0.5	0	0	1.5		23
Ulug, 2008 [84]	2	2	2	2	1		2		61

NOTE: Blank cells represent categories that were not applicable to the question.

Table 16. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other Than Sickle Cell Disease

Author, year	Intervention (N)	Mean drug (D) or follow-up (F) duration	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
Bloch, 2006[85]	Indinavir, ritonavir, ddI, and either stavudine or lamiduvine + HU (35) Indinavir, ritonavir, ddI, and either stavudine or lamiduvine (33)					Indinavir, ritonavir, ddI, and either stavudine or lamiduvine + HU: 1 Indinavir, ritonavir, ddI, and either stavudine or lamiduvine: 0					Indinavir, ritonavir, ddI, and either stavudine or lamiduvine + HU: CMV esophagitis, (3) renal colic, (20) pneumonia, (3) Indinavir, ritonavir, ddI, and either stavudine or lamiduvine: Neuropathy, (3) rectal tear, (3) renal colic, (3)
Broustet, 1991[86]	HU (26) IFN (24)	HU: D: 20.4 months IFN: D: 13.9 months				HU: 0 IFN: 1				HU: 0 IFN: 1	IFN: • Flu-like, 1 • CNS disturbance, 2 • Thyroid insufficiency, 2

Table 16. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other Than Sickle Cell Disease (continued)

Author, year	Intervention (N)	Mean drug (D) or follow-up (F) duration	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
Burnett, 2007[87]	HU (99) Low-dose cytarabine (103) HU (8 weeks) (38) Low-dose cytarabine (8 weeks) (40)	HU and low-dose cytarabine: Unclear HU and low-dose cytarabine (8 weeks): (8 weeks)	HU: 26 (26) Low-dose cyta-rabine: 27 (26) HU (8 weeks): 14 (38) Low-dose cyta-rabine (8 weeks): 16 (39)								HU: ****** (Nausea/emesis 0.6, Alopecia 0.2, Oral 0.5, Diarrhea 0.5, Cardiac 0.5) HU (8 weeks): Infection n = 8, Hemorrhage n = 1, Stroke n = 0, Cardiac n = 1, Renal n = 1, Other n = 3, Resistant/progressive disease n = 14 Low-dose cytarabine (8 weeks): Infection n = 18, Hemorrhage n = 2, Stroke n = 1, Cardiac n = 0, Renal n = 2, Other n = 3, Resistant/progressive disease n = 14
Cortelazzo, 1995[88]	HU (56) None (58)	HU: D: 27 months			HU: 0 None: 0		HU: 0 None: 0			HU: 0 None: 0	
Finazzi, 2000[89]	HU (56) No myelo-suppressive agent at randomization (58)	HU: Median F: 73 months (393) No myelo-suppres-sive agent at randomi-zation: Median F: 73 months (1294)						HU: 7 (13) No myelo-suppressive agent at randomiza-tion: 1 (1.7)*****			

Table 16. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other Than Sickle Cell Disease (continued)

Author, year	Intervention (N)	Mean drug (D) or follow-up (F) duration	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
Frank, 2004[90]	ddI mono (28) HU (low dose) with/without ddI (53) HU (high dose) with/without ddI (50)	ddI mono: D: 6 months		ddI mono: 3 (11) HU (low dose) with/ without ddI: 10 (19) HU (high dose) with/ without ddI: 20 (40)*	ddI mono: 0 HU (low dose) with/without ddI: 1 (2) HU (high dose) with/without ddI: 9 (18)†	ddI mono: 0 HU (low dose) with/without ddI: 0 HU (high dose) with/without ddI: 3 (6)					ddI mono: Grade 3 chemistry or more, 3 (11) HU (low dose) with/without ddI: Grade 3 chemistry or more, 7 (13) HU (high dose) with/without ddI: Grade 3 chemistry or more, 4 (8)
Harrison, 2005[91]	Aspirin + HU (404) Anagrelide + aspirin (405)	Aspirin + HU: Median F: 39 months (1272)	Aspirin + HU: 4§§§§ Anagrel-ide + aspirin: 3‖ ‖ ‖ ‖				Aspirin + HU: 6 Anagrelide + aspirin: 4¶¶¶¶				Aspirin + HU: Myelofibrosis, 5 Anagrelide + aspirin: Myelofibrosis, 16####

Table 16. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other Than Sickle Cell Disease (continued)

Author, year	Intervention (N)	Mean drug (D) or follow-up (F) duration	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
Havlir, 2001[92]	IDV, ddI, d4T, + HU (68) IDV, ddI, d4T + placebo (68) IDV, ZDV (or d4T), 3TC (66) ABC, EFV, ddI (24)	IDV, ddI, d4T, + HU: F: 40 weeks	IDV, ddI, d4T, + HU: 3 IDV, ddI, d4T + placebo: 0 IDV, ZDV (or d4T), 3TC: 0							ABC, EFV, ddI: 3	IDV, ddI, d4T, + HU: GI upset, 2 Pancreatitis, 4 Asymptomatic amylase elevation, 2 IDV, ddI, d4T + placebo: GI upset, 1 Pancreatitis, 3 ABC, EFV, ddI: GI upset, 10 Neurological/ psychiatric, 12 Nasal symptoms, 2 Endocrine or metabolic, 3 Arthralgia, 1 Fatigue, 2 Neuropathy, 1
Hehlmann, 1993[93]	HU (216) Busulfan (225)	HU: Median F: 2.03 years									HU: Long lasting bone marrow aplasia, 0 (denominator = 209) Long lasting bone marrow aplasia, unknown (denominator = 204)
Hehlmann, 1994[94]	HU (194) IFN (133) Busulfan (186)	HU: Median F: 3.4 years						HU: 1 (0.5) IFN: 2 (1.5) Busulfan: 2 (1.0)			HU: Fever, 1 (0.5)

Table 16. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other Than Sickle Cell Disease (continued)

Author, year	Intervention (N)	Mean drug (D) or follow-up (F) duration	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
Hehlmann, 2003[95]	HU (308) IFN + HU (226)	HU: F: 7.3 years IFN + HU: Follow-up: 7.9 years								HU: 29/30 (9.4) IFN + HU: 64/22 (28.3)	HU: GI upset, 60 (19.5) (denominator = 304) Flu-like, 38 (12.3) Neurological/ psychiatri c, 19 (6.2) Cardiac/pulmonary symptoms, infections, wt. loss, Lab findings, BM aplasia, 53 (17.2) IFN + HU: GI upset, 88 (38.9) (denominator = 222) Flu-like, 146 (64.6) Neurological/ psychiatri c, 82 (36.3) Cardiac/pulmonary symptoms, infections, wt. loss, lab findings, BM aplasia, 92 (40.7)
Kiladjian, 2006[96]	HU (123) Pipobroman (134)	HU: Followup: 14 years Pipo-broman: Followup: 11 years					HU: 15†† Pipo-broman: 25‡‡				
Loening, 1981[97]	HU (40) Cyclophos-phamide (43) Methyl-CCNU (38)	HU: NR			HU: 2/28 (7) Cyclophos-phamide: 2/34 (5) Methyl-CCNU: 11/27 (41)	HU: 8/28 (29) Cyclophos-phamide: 11/34 (26) Methyl-CCNU: 9/27 (33)					HU: GI upset, 13 (46) (denominator = 28) Cyclophosphamide: GI upset, 20 (46) (denominator = 43) Methyl-CCNU: GI upset, 11(41) (denominator = 27)

Table 16. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other Than Sickle Cell Disease (continued)

Author, year	Intervention (N)	Mean drug (D) or follow-up (F) duration	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
Najean, 1997[98]	HU (150) Pipobroman (142)	HU: F: 1 - 17 years					HU: NRby arm§§§ Pipo-broman: NRby arm¶¶¶	HU: 10‖ ‖ ‖ Pipo-broman: 6###	HU: 12 (9) Pipo-broman : 1	HU: 10 (7) Pipo-broman: 5 (4)	HU: GI upset, 9 (7) Myelofibrosis, 26, 40% at the 16th year Cystitis, 3 (2) Stomatitis, 13 (10) Pipobroman: GI upset, 19 (17) Myelofibrosis, 3 Stomatitis, 4 (4)
No author, 1998[99]	HU alone (95) IFN and HU if needed (100)	HU alone: F: 51 months								HU alone: 1 IFN and HU if needed: 3	HU alone: Fever, 2 Accelerated disease/blast crisis, 52 IFN and HU if needed: Flu-like, 7 Neurological/ psychiatric,6 Vasculitis, 1 Accelerated diesease/blast crisis, 37
Rutschmann, 1998[100]	ddI, stavudine + HU (72) ddI, stavudine + placebo (72)	ddI, stavudine + HU: F: 24 weeks		ddI, stavu-dine + HU: 14‡ ddI, stavu-dine + placebo: 3/ 25	ddI, stavudine + HU: 8§ ddI, stavudine + placebo: 3					ddI, stavudine + HU: 5‖ ddI, stavudine + placebo: 4	ddI, stavudine + HU: GI upset, 16 Fatigue, 10 Neuropathy, 18¶ Diarrhea, 15 ddI, stavudine + placebo: GI upset, 11 Fatigue, 2 Neuropathy, 10 Diarrhea, 9

Table 16. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other Than Sickle Cell Disease (continued)

Author, year	Intervention (N)	Mean drug (D) or follow-up (F) duration	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
Rutschmann, 1998[101]	ddI, stavudine + HU (72) ddI, stavudine + placebo (72)	ddI, stavudine + HU: D: 12-48 weeks F: 48 weeks		ddI, stavu-dine + HU: 11/ unclear ddI, stavu-dine + placebo: 3**	ddI, stavudine + HU: 7 ddI, stavudine + placebo: 1††						ddI, stavudine + HU: Fatigue, 10 Diarrhea, 15 Paraesthesia, 29 ddI, stavudine + placebo: Fatigue, 2‡‡ Diarrhea, 9§§ Paraesthesia, 14‖ ‖
Rutschmann, 2000[102]	ddI, stavudine + HU (72) ddI, stavudine + placebo (72)	ddI, stavudine + HU: F: 24 months		ddI, stavu-dine + HU: 18¶¶ ddI, stavu-dine + placebo: 8	ddI, stavudine + HU: 29## ddI, stavudine + placebo: 8			ddI, stavudine + HU: 4 Kaposis' sarcoma*** ddI, stavudine + placebo: 1 Kaposi's sarcoma		ddI, stavudine + HU: 8 ddI, stavudine + placebo: 5	ddI, stavudine + HU: GI upset, 20††† Hair loss, 1 Fatigue,16 Neuropathy, 28‡‡ Diarrhea, 23 Mucositis, 5 ddI, stavudine + placebo: GI upset, 6 Hair loss, 1 Fatigue, 5 Neuropathy, 10 Diarrhea, 15
Seminari, 1999[103]	ddI + HU (40) ddI (21)	ddI + HU: F: 40 weeks ddI: D: 24 weeks		ddI + HU: 1 ddI: 0	ddI + HU: 1 ddI: 0	ddI + HU: 1 ddI: 0					ddI + HU: Hair loss, 2 hyperamylasemia, 1 hypertryglyceridemia, 1 ddI: GI upset, 1 Hyperamylasemia, 1 Hypertryglyceridemia, 1
Swindells, 2005[104]	ABC, EFV, ddI + HU (30)	ABC, EFV, ddI + HU: F: 48 weeks								ABC, EFV, ddI + HU: 5	ABC, EFV, ddI + HU: GI upset, 28 Neurological/ psychiatric, 23 Endocrine or metabolic, 7 Arthralgia, 2 Fatigue, 6 Neuropathy, 4

Table 16. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other Than Sickle Cell Disease (continued)

Author, year	Intervention (N)	Mean drug (D) or follow-up (F) duration	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
Stephens, 1984[105]	HU (69) Adriamycin + cyclophospha-mide (68)	HU: NR Adriamy-cin + cyclophos-phamide: NR			HU: 11/68 (16) Adriamycin + cyclophos-phamide: 9/68 (14)						

* p = 0.007 (comparing arms 2 and 3)

*** p = 0.2

† p = NS †††p = 0.006

‡ p = 0.04 for grade 1, ns for 2, 3, (denominator = 36) §§§ Risk = 10% at 13th year (denominator = 150)
§ p = 0.03 for grade 1, ns for 2 and 3 ‖ ‖ ‖ Risk = 15% at 14th year, Risk = 1.1% per year
‖ p = 0.7 ¶¶¶ Risk = 10% at 13th year (denominator = 142)
¶ p = 0.09 ### Risk = 15% at 14th year, Risk = 1.1% per year
# n = original assignments, please see associated text for number of patients that **** p = 0.0321 (this symbol doesn't appear in the table)
crossed over. †††† 6 (40%) occurred after the 12th yr of f/u, (denominator = 123)
** p = 0.04, (denominator for this outcome unclear given crossover) ‡‡‡‡ 11 (44%) after the 12th yr of follow-up (denominator = 134)
††p = 0.03 §§§§ Death from transformation

‡‡ p = 0.02 ‖ ‖ ‖ ‖ It is unclear why this only represents 157 patients when it is a follow-up of the §§ p = 0.2 original study 123. No information on patients lost to follow-up is given
‖ ‖p = 0.008 ¶¶¶¶ (OR 0.67, CI, 0.20-0.33) p = NS ¶¶ p = 0.08 #### (OR 2.92, CI, 1.24 - 6.86) p = 0.01 ## p = 0.001 ***** p = 0.0321, ******the severity of toxicity according to National Cancer Institute

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BM = bone marrow; CCNU = lomustine; CI = confidence interval; CMV = cytomegalovirus; CNS = central nervous system; d4T = didehydrodeoxythymidine; ddI = didanosine; EFV = efavirenz; ET = essential thrombocytopenia; GI = gastrointestinal; HU = hydroxyurea; IDV = indinavir; IFN = interferon; NR = not reported; NS = not significant; OR = odds ratio; PV = polycythemia vera; wt = weight; ZDV = zidovudine.

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease*

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombocyt openia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Ansari, 2007[106]	HU (21)	F: 24 months	1								4 mild myelo-suppression, 2 diarrhea,
Bernasconi, 2002[107]	HU only (23) Pipobroman (106) No treatment (26)	Median F: 104 months (range, 8-240) for all three groups					HU only: 4‖ ‖ Pipobroman: 4¶¶ No treatment : 0				
Chim, 2005[108]	HU alone (224) Melphalan + HU (4) Phosphorus + HU (3)	F: 10 years					HU alone: 3 (1.3) Melphalan + HU: 2 Phosphorus + HU: 0				HU alone: Myelofibrosis, 6 Melphalan + HU: Myelo-fibrosis, 1
D'Adda, 2008[109]	HU (13)	F: 57 months [15-219]		8 (62)					2 (15)		Thrombo-cytosis: 2 pts
Donovan, 1984[110]	HU no prior treatment (59) HU after prior myelo-suppressive therapy (59)	HU no prior treatment: F: 61 weeks to 171 weeks HU after prior myelo-suppressive therapy: F: 193 weeks					HU no prior treatment: 2 HU after prior myelo-suppressive therapy: 1				

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Duletic-Nacinovic, 2000[111]	HU (72) Busulfan (109) 8 varieties prior chemo: two patients had no prior therapy (10)	HU: F: Median = 32 months Busulfan: F: Median = 31 months	8 varieties prior chemo: two patients had no prior therapy: 7/9	HU: 2 Busulfan: 8		HU: 0 Busulfan: 2				HU: 0 Busulfan: 2	Busulfan: Lung fibrosis, 3 Amenor-rhea, 2
Finazzi, 2005[112]	HU only (742) Any other cytoreductive drug (227) No drug or interferon α only (669)						HU only: 6 Any other cyto-reductive drug: 11 No drug or interferon α only: 5				
Fruchtman, 1997[113]	HU (51) Phlebotomy (134)	HU: F: 795 weeks Phlebotomy: NR	HU: 16 (31.4)‡‡ Phlebot-omy: 54 (40.3)				HU: 5 (9.8)§§ Phlebotomy: 5 (3.7)				HU: Spent phase, 4 Phlebotomy: Spent phase, 15

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Gangat, 2007[114]	HU only (165) Anegralide or IFN α only (63) Exposure to single agent cytotoxics other than HU (21) No drug exposure (181) Anagrelide or IFN + HU (128) Other cytotoxics + HU (47)	HU only: Median F: 84 months (0-424)					HU only: 5 Anegralide or IFN α only: 1 Exposure to single agent cytotoxics other than HU: 3 No drug exposure: 4 Anagrelide or IFN + HU: 2 Other cytotoxics + HU 5				
Italia, 2009[115]	HU (79)	Median F: 22 months [20-24]		16 (20)							
Italia, 2010[116]	HU (13)	F: 20 months		Incidence NR							
Kaplan, 1986[117]	HU (51) Phlebotomy (134)	HU: D: Median 245 weeks (range: 5-389 weeks) Phlebotomy: NR					HU: 3 (5.9) Phlebotomy: 2 (1.5)††				
Koren, 2008[118]	HU (18)	D: 46 +/- 26 months, (range 6-96)		3							

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Kosaryan, 2009[119]	HU (297)	D: 5.2 +/- 2 years [0.5-9]									Nausea 3, palpitation 9, transient Leukopenia 18,
Latagliata, 2009[120]	HU (symptomatic pts) (32) HU (>70 yrs of age) (33) HU (> or = 4 points on study scoring system for risk, score incr') (32) HU (<4 points after 28 days of dx) (24) Non HU (47)	F: 106 months [59.9-135.6]	16 (9.5)				4 (3.3) Non HU: 1 (2.1)	9 (7.4) Non HU: 1 (2.1)	5 (4.1)		HU: Thrombosis: 5 (7) HU (>70 yrs of age): Thrombosis: 4 (12.5) HU (> or = 4 points on study scoring system for risk, score incr'): Thrombosis: 4 (12.5) HU (<4 points after 28 days of dx) : Thrombosis: 5 (7)

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Lim, 2009[121]	INF-alpha (40) HU (26) Imatinib mesylate (22) 2-Chlorodeoxy-adenosine (22)	INF-alpha: D: 12 months (median) [1-65] HU: D: 31.5 months (median) [5-50] Imatinib mesylate: D: 19.6 months (median) [6-96] 2-Chlorodeoxy-adenosine: Median D: 11 months [3-74]			INF-alpha: Was a major toxicity. Otherwise not specified						INF-alpha: Major tox included: fatigue and depression HU: Major tox was myelo-suppression Imatinib mesylate: Major tox included: diarrhea and edema 2-Chloro-deoxy-adenosine: Major tox included: infection and myelo-suppression

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Mavrogianni, 2002[122]	PV: HU therapy (34) ET: HU therapy (30) PV: HU and busulfan (1) ET: INF α (4)	PV: HU therapy: D: 86 [36-195] months ET: HU therapy: D: 79 [36-162] months PV: HU and busulfan: D: 44 months on HU followed by 86 months on busulfan ET: INF α: D: 105 [91-123] months					PV: HU therapy : 2 (5.7) ET: HU therapy: 1 (3.3)			PV: HU and busulfan: 1	
Mtvarelidze, 2008[123]	HU (6)	F: 60 months									Erythro-poietic toxic reaction: 1

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Najean, 1996[124]	HU only§ (104) Pipobroman (98) 32P+HU maintenance (174) 32P without maintenance (221)	HU only§: Median followup: 6.7 years Pipobroman: Median followup: 6.7 years 32P+HU maintenance: D: 1-15 years Median 10.5 years 32P without maintenance: D: 1-15 years, Median 10.5 years					HU only§: 13% at 12y f/u‖ Pipobroman: 14% at 12y f/u‖ 32P+HU maintenance: 19% at 10y f/u# 32P without maintenance: 10% at 10y f/u	HU only§: 9% at 10y f/u¶ Pipobroman: 9% at 10y f/u¶ 32P+HU maintenance: 29% at 12y f/u‖ 32P without maintenance: 15% at 12y f/u‖ **			HU only§: Myelo-fibrosis, 17% at 12 year f/u 32P+HU mainte-nance: Myelo-fibrosis, 16% at 10 year f/u; 23% at 14 year f/u 32P without mainte-nance: Myelo-fibrosis, 10% at 10 year f/u; 19 at 14 year f/u

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Nielsen, 2003[125]	HU (36) No drug treatment (21) Busulfan alone (4) Busulfan + HU (18) Anagrelide + HU (1) Busulfan, IFN + HU (1) Busulfan, anagrelide + HU (1) IFN + HU (1)	HU: F: 7.8 years (follow-up for all patients that received HU) No drug treatment: F: 10.5 years (this is follow-up for all patients that did not receive HU) Busulfan, IFN + HU: 62 Busulfan, anagrelide + HU: 84 IFN + HU: 21						HU: 5 No drug treatment: 1 Busulfan Alone: 0 Busulfan + HU: 4 Anagrelide + HU: 0 Busulfan, IFN + HU: 1 Busulfan, anagrelide + HU: 1 IFN + HU: 1				
Ogbogu, 2009[126]	Steroids (179) HU (64) INF a (46) Cyclosporine (11) Imatinib (68)	Steroids: D: 2 months-20 yrs HU: NR INF a: NR Cyclosporine: NR Imatinib: NR	Steroids: 4								

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Palandri, 2009[127]	HU (205) Non HU (133)	F: median = 9.5 years [3-28.5]								HU: 3 (1.4) Non HU: 2 (1.5)	HU: Extra-hema-tological toxicity 6, Hyper-transamina-semia 3, Hema-tological toxicity 5 Non HU: Extra-hema-tological toxicity 6, Hyper-transamina-semia 3,Hema-tological toxicity 5

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Radaelli, 2008[128]	HU only (116) Alkylating agents (ALK) (busulfan or melphalan) (38) ALK followed by HU (40) No treatment (137)	F: median = 108 months									HU only: second malig-nancies 13 Alkylating agents (ALK) (busulfan or melphalan): second malig-nancies 10 ALK followed by HU: second malig-nancies 10 No treatment: second malig-nancies 10
Randi, 2005§[129]	HU (152)	Median 4.33 years aspirin (n = 88), ticlopicine (n = 11), oral anticoagulants (n = 12), 8.13 years	3 (1.97)			5 (0.03 29)	3, (1.97)		4 (2.6)		Cutaneous allergic reaction and mild pancyto-penia, 1; Allergic reaction and transient liver failure, 1; Fever above 39°C, 2

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Randi, 2005[130]	HU (129)	F: 7.18 years				2/129	3	1	4	3	CV complica-tions, 4 Coronary complica-tions, 5 Fever above 39°C, 2
Randi, 2008[131]	HU (27) Non HU (27)	HU: F: [24-144] months Non HU: F: [12-216] months	HU: 2 Non HU: 1								HU: In 5 pts, "major" HU side effects occurred and tx was stopped
Ranjan, 2007[132]	HU (15) Methotrexate (15)	F: 12 weeks								HU: 2 (13) Metho-trexate: 5 (33)	The side effects in both groups were mild and did not require d/c of tx. No pt developed hepatic or hematologic toxicity due to any of the drugs

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Sterkers, 1998[133]	HU alone (201) HU + other agents (50) 32P alone (29) 32P + other agents (11) Busulfan alone (35) Busulfan + other agents (6) Pipobroman alone (12) Pipobroman + other agents (31) No treatment (31)	HU alone: Median F: 98 months (22 - 265)					HU alone: 7 (3.5) HU + other agents: 7 (14) 32P alone: 2 (7) 32P + other agents: 1 (9) Busulfan alone: 1 (3) Busulfan + other agents: 1 (17) Pipobroman alone: 0 Pipobroman + other agents: 5 (16) No treatment: 0				

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Taher, 2010[134]	Non HU (382) HU (202)								Non HU: 44 (11.5) HU: 2 (1)		Non HU: Extra-medullary hemato-poiesis 91 (23.8%), pulmonary HTN 53 (13.9%), 2^0 heart failure 12 (3.1%), Thrombosis 65 (17%), Cholelithiasis 80 20.9%), Abnormal LFTs 36 (9.4%), DM 99 (2.6%), Osteoporosis 132 (34.6%), Hypo-gonadism 44 (11.5%) HU: Extra-medullary hemato-poiesis 33 (16.3%), pulmonary hypertension 11 (5.4%), secondary heart failure 13 (6.4%), Thrombosis 17 (8.4%), Cholelithiasis 20 (9.9%), Abnormal LFTs 21 (10.4%), Hypo-gonadism 57 (28.2%)

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Urabe, 1990[135]	HU (134)	NR								1	Liver dysfunction, 1 GI upset, 1
Vassallo, 2001[136]	HU (158)	D: Median = 38 months						5		21‡	
Weinfeld, 1994[137]	PV: HU (30) ET: HU (10) MF: HU (10)	NR			PV: HU: (30) ET: HU: (30)		PV: HU: 3 ET: HU: 1 MF: HU: 3				PV: HU: Chromo-somal anomalies, 4/11; platelet count > 6x109/l ET: HU: Chromo-somal anomalies, 1/5; platelet count > 6x109/l MF: HU: Chromo-somal anomalies, 2/3
West, 1987[138]	HU only (100)	D: 3-216 months, mean 64.9 [3-21] F: 20 year observation					2 (2)	1 (1)		1	Splenic infarction, 1 Myelo-fibrosis, 6

Table 17. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other Than Sickle Cell Disease* (continued)

Author, year	Intervention (N)	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration (%)	Other, n (%)
Yin, 2006[139]	15 -HU 1-imatinib (16)	D: HU, 2 weeks-31 months before translocation; D: imatinib alone, 3 months	8/15								
Zamani, 2009[140]	HU (49)	F: 60 months		1 (2)							

* Denominators = N unless otherwise specified.

† Unless otherwise specified

‡ HU therapy was discontinued in all 21 patients showing toxicity, and all cutaneous ulcers healed within a median period of 9 months. § 12 patients originally assigned to the HU arm were switched to pipobroman, and 5 patients on the pipobroman arm were switched to the HU arm. ‖ Actuarial risk ¶ Observed risk # Reported as "significant" when compared to no maintenance arm** p < 0.01 at 10 year f/u compared to Arm 3

†† p > 0.25

‡‡ p = 0.0718

§§ p = 0.0973

‖‖ Incidence rate ratio HU v PI 6.15, CI, 1.4-26.99, 5-year CI = 8.09%, 10-year CI = 15.53%, 15-year CI = 22.37% (where CuI is cumulative incidence, p for IRR = 0.0198

¶¶ 5-year CuI = 1.97%, 10-year CuI = 3.89%, 15-year CuI = 5.78%

32P = radioactive phosphorus; CV = Cardiovascular; ET = Essential thrombocytopenia; f/u = followup; GI = Gastrointestinal; HU = Hydroxyurea; IFN = Interferon; MF = Myelofibrosis; MPD = Myeloproliferative Disorder; NR = Not reported; PV = Polycythemia vera, HTN = hypertension, LFT = liver function test, DM = diabetes mellitus.

Table 18. Hydroxyurea Toxicity Results From Case Reports in Disease Other Than Sickle Cell Disease

Outcome	# of case reports	Females/ males	Underlying disease %	Median weeks on HU until toxicity	# of case reports with certain causality	# of reports with probable causality	# of reports with possible causality	# of reports with unlikely causality
Alopecia	1	1/0	CML: 100	16			1	
Alveolitis	2	0/2	CML: 50, MPD: 50	4		1	1	
Arthritis	1	0/1	CML: 100	12			1	
Azoospermia or decreased sperm motility	4	04	ET: 50, PV: 50	470, 338	2	1	1	
Behcet's disease	2	2/0	CML :100	91			1	1
Colitis	1	0/1	CML: 100	2		1		
Cytopenia	5	3/2	HIV: 40, PV: 20, MPD: 40	12, 312		1	4	
Eyelid changes	1	0/1	CML: 100	NR		1		
Falsely elevated HbA1c	1	0/1	PV: 100	NR				1
Fever	16	7/9	ET: 69, CML 13, other: 13, MPD: 6	3, 676	14		2	
Gangrene of toes	2	1/1	CML: 100	175			2	
Glioblastoma multiforme	1	1/0	MPD: 100	150			1	
Hemolytic anemia	2	1/1	ET: 50, MPD: 50	413		1	1	
Hepatitis	6	2/4	ET: 33, PV: 33, Psoriasis: 33	27	3	1	2	
Interstitial Pneumonitis	5	1/4	CML: 40, ET: 40, MPD: 20	16	1	3	1	
Leg ulcer	74	31/42, one unclear	CML: 43, ET 22; PV: 24, MPD: 8, one unclear	220, 182	6	35	33	
Leukemia	36	17/19	ET: 61, PV: 22, MPD: 12, Hyper-eosinophilia: 6	300, 260			33	3
Limbal stem cell deficiency (cornea)	1	0/1	CML: 100	104	1			
Lymphoma	2	1/1	ET: 50, Hyper-eosinophilia: 50	450			2	

Table 18. Hydroxyurea Toxicity Results From Case Reports in Disease Other Than Sickle Cell Disease (continued)

Outcome	# of case reports	Females/ males	Underlying disease %	Median weeks on HU until toxicity	# of case reports with certain causality	# of reports with probable causality	# of reports with possible causality	# of reports with unlikely causality
Melanoma	1	0/1	ET: 100	64			1	
Meningioma	1	1/0	ET: 100	520			1	
Multiple myeloma	1	1/0	ET: 100	360			1	
Nail change	15	11/4	CML: 33, ET: 20, Psoriasis: 7, MPD: 40	104, 45.5		6	9	
Neuromuscular disorder	1	0/1	CML: 100	4			1	
Oral ulcers	4	0/4	ET: 25, Leukemia: 75	116		2	2	
Pruritis	1	1/0	PV :100	5	1			
Pulmonary Fibrosis	1	1/0	PV: 100	16			1	
Dermatological changes	35	20/15	CML: 66, ET: 6, PV: 24, Leukemia: 3, MPD: 3	222, 780		19	16	
Sarcoidosis	1	0/1	ET: 100	16			1	
Sarcoma	1	0/1	ET: 100				1	
Skin cancer	29	10/19	CML: 38, ET: 27, PV: 27, MPD: 7	376, 403	1	6	22	
SLE	1	1/0	Psoriasis: 100	160		1		
Soft-tissue Nodule	1	0/1	MPD: 100	32		1		
Thrombotic microangiopathy	1	1/0	CML: 100	72			1	
Tumor-lysis	4	1/3	CML: 25, Leukemia: 50, PV: 25	0.56			4	
Ulcer (surgical site)	1	1/0	PV: 100	300		1		
elevations in liver function tests	1	0/1	PV:100	1	1			
neutropenia	2	1/1	SE: 100	Unclear			1	
Decreased platelet count	1	1/0	SE:100	Unclear			1	

Table 18. Hydroxyurea Toxicity Results From Case Reports in Disease Other Than Sickle Cell Disease (continued)

Outcome	# of case reports	Females/ males	Underlying disease %	Median weeks on HU until toxicity	# of case reports with certain causality	# of reports with probable causality	# of reports with possible causality	# of reports with unlikely causality
Erythema induratum (Bazin disease) in her legs / erythematous maculopapular rash	1	1/0	ET: 100	260		1		
Dermatomyositis	1, 1	1/1	MPD: 100	442		1	1	

[68]: for papers published before July, 2007
[72, 141-158]: July, 2007- present

CML = chronic myelogenous leukemia; ET = essential thrombocytopenia; HIV = human immunodeficiency virus; HU = hydroxyurea; MPD = myeloproliferative disorders; NR = not reported; PV = Polycythemia Vera; SLE = Systemic lupus erythematosus. * WHO causality assessment

HU = hydroxyurea; NR = not reported; MPD = myeloproliferative disorder;

A reaction was rated as “certain” if all four criteria for causality were fulfilled: (1) a plausible time relationship between drug administration and an event; (2) an absence of a concurrent disease that might have caused the event; (3) a reasonable response to drug withdrawal; and (4) existence of a re-challenge or a demonstrated biological explanation. A reaction was rated as "probable" if criteria 1, 2, and 3 were fulfilled and “possible if only criterion 1 was met and information on criterion 3 was lacking or unclear. A reaction was rated as "unlikely" if criterion 1 was not met and if other drugs, chemicals, or underlying disease provided a plausible explanation for the reaction.

1. Is the time relationship from drug administration to the event plausible for causality to be established?
2. Is there an absence of concurrent diseases or other drugs that may have caused the event?
3. Is there a reasonable response to drug withdrawal?
4. Is there the existence of a re-challenge in this report or a demonstrated biological/pharmacological explanation?

Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Armstrong, 1992[159]	Provider provision of pain medication Provider report	Physicians (pediatric residents), Nurses Unknown	92	Hospital visits	NR	Provider attitudes, professional experience and training	Nurses, but not pediatric residents, recommended lower pain medication doses for frequently, as opposed to occasionally, hospitalized children as described in hypothetical history vignettes. However, there were no differences in pain ratings between nurses and residents across the vignettes. There were no significant correlations between nurse or resident pain ratings or medication decisions and their attitudes and beliefs about pain in children.
Barakat, 2002[160]	General adherence to treatment regimens Provider report, patient report, family report, administrative data	Patients (Children/ Caregivers) Unknown	81	NR	Greater parental/ family knowledge, family problem-solving effort, higher family income	NR	In multivariate models, greater SCD knowledge (p = 0.032) and greater family effort in solving family problems (p = 0.037) were significantly associated with higher medical staff rating of patient/ family adherence to treatment regimens. Greater family income was marginally associated with higher medical staff ratings of adherence (p = 0.053).
Belgrave, 1994[161]	Appointment-keeping Patient report	Patients (Adults) Washington, DC, USA	49	NR	Social support	NR	Social support, defined in this study as the frequency of supportive and helpful behaviors performed by others, was positively correlated with self-report of medical appointment keeping (r = 0.47, p 0.05). Patients with greater social support had better self-reported rates of keeping medical appointments

Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Crosby, 2009[162]	Examining perceived barriers to clinic attendance and strategies to overcome these barriers	Patients (children, adolescents) Midwest, USA	45	Competing activities involving school or peers; birthdays, homework	Education about the importance of attending routine clinic visits, interventions to decrease forgetting (e.g., phone call reminders or text messaging), Scheduling appointments to accommodate busy schedules/ scheduling conflicts providing teen-friendly clinic environments, and using technology		Adolescents identified competing activities, health status, patient-provider relationships, adverse clinic experiences, and forgetting as barriers to clinic attendance. Calendars/reminders and parent reminders were the most commonly reported strategies to facilitate clinic attendance. Adolescents also reported the need for flexible scheduling and improved patient-provider communication
Elliot, 2001[163]	Patient adherence to prophylactic antibiotics Family report, Administrative records	Patients (Children/ Caregivers) Unknown location	50	More children at home	More adults at home, having a car	Patient age, parental education	A higher number of adults living in the home and having a car were positively associated with compliance ($p < 0.01$). A higher number of children in the home was negatively associated with compliance ($p < 0.01$). The number of days between refills tended to increase as the child's age increased ($p = 0.15$). Maternal education was not significantly associated with compliance ($p = 0.25$). The authors assessed the utility of the Health Belief Model (HBM) in predicting parental compliance with prophylactic penicillin administration and did not find that any of the assessed variables (parent's perceptions of the seriousness of infection in young children with SCD, the perceived susceptibility of their child to infection, the perceived benefit of prophylactic penicillin in preventing infection, and the perceived burden of penicillin administration) were significantly associated with compliance after adjustment for demographic factors ($p = 0.61$).

Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Hankins, 2007[32]	Patient decision to initiate HU Patient report, family report	Patients (Children, caregivers)/ Memphis, TN, USA	30		Perceived safety and efficacy	Parental age, sex, # of children, parent's rating of child's HRQOL, frequency of VOC in prior 2 years	In this study of patient and parental treatment decisions, after hearing non-biased information about all three potential treatments, the majority of patients and parents (70%) chose HU therapy over chronic transfusion (17%) and stem cell transplantation (10%) ($p < 0.001$). The perceived efficacy and perceived safety of potential treatment options were the two most commonly cited factors affecting parental treatment preferences for their kids (~80% of respondents each). Health related quality of life (HRQOL) and number of vasoocclusive crisis events were not associated with treatment preference. There was disagreement over treatment preference in 3 out of 7 patient-parent dyads.
Haque, 2000[164]	Use of routine health services Patient report, administrative data	Patients (Adults and Children/ Caregivers) North Carolina, USA	1189	Greater community socioeco-nomic distress	Rural geographic region	Distance to clinic, interference of disease in daily life, level of medical problems	Patients living in rural areas were estimated to have greater utilization of comprehensive sickle cell services than patients living in urban areas after adjustment for socioeconomic distress, interference of sickle cell disease in their daily lives, their self-reported level of medical problems, their distance to a comprehensive clinic, and a term representing the interaction of distance to a clinic and their level of socioeconomic distress ($p < 0.001$). In this same model, patients living in areas with more socioeconomic distress were estimated to have less utilization of services ($p = 0.04$) after adjustment for the other factors. None of the other variables in the model were significantly associated with utilization.
Jensen, 2005[165]	Patient adherence to prophylactic antibiotics Family report	Patients (Children/ Caregivers) USA	97	NR	Caregiver knowledge for children <11 yrs, no child history of transfusions	History of stroke, hospital visits, # of missed appointments	In the overall sample, caregiver knowledge of SCD did not correlate with adherence with recommended SCD preventative behaviors ($r = 0.16$, $p = 0.12$). In post-hoc analyses, however, the authors found that caregiver knowledge of SCD was positively associated with adherence for children 11 years of age and younger, but not for children 12 and older ($p < 0.05$).

Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Labbe, 2005[166]	Provider provision of pain medication Provider report	Physicians 7 federally funded comprehensive SCD centers in the USA	109	Negative provider attitudes	Fewer provider years in practice, provider female gender		Physician characteristics and attitudes may affect the quality of pain management delivered to patients with SCD. The earlier the year of graduation from medical school, the more likely a physician was to believe that opioids play major role in the development of addiction ($r = -0.32$, $p < 0.001$), and also that drug addiction should be a primary concern when treating SCD patients ($r = -0.26$, $p < 0.008$). Female physicians were more likely than male physicians to believe that the primary focus of treatment for a sickle cell crisis should be adequate pain relief ($r = -0.20$, $p < 0.04$). Physicians who believed drug addiction should be a primary concern were less likely to believe the primary focus of treatment should be adequate pain relief ($r = -0.20$, $p < 0.0037$).
Lanzkron, 2008[167]	Providers' awareness of the NHLBI recommendations regarding HU prescribing, whether these recommendations have changed providers' practices & how these providers prescribed HU	Health care providers (Adult pts) Location unclear	48	Provider concerns to prescribe HU, lack of time and resources to adequately explain the risks and benefits	NR	NR	94% heard about the NHLBI recommendations, 81% read it, 76% of whom read it either somewhat or completely agreed with it, while19% either somewhat or completely disagreed with it, and 5% had no opinion. 45% did not change their practice, 29% moderately changed, 13% significantly changed

Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Logan, 2002[168]	Use of routine health services Patient report, family report, administrative data	Patients (Children/ Caregivers) Unknown	70	NR	Illness-related stress, greater parental/ family knowledge	Parent/ adolescent relationship, disease severity, stressful life events, clinical maladjustment	The authors developed a multivariate model predicting the use of routine health services (scheduled clinic visits, calls to clinic, information seeking from clinic, management of pain symptoms at home). The frequency of illness-related stress accounted for the largest individual portion of the explained variance in routine service use (partial $r = 0.41$, $p < 0.001$). Having more frequent illness-related stress was associated with greater use of routine services. Greater parental knowledge of SCD also accounted for a significant portion of the variance in routine service use and predicted more use of routine services (partial $r = 0.33$, $p < 0.001$). Parental reports of the parent-adolescent relationship, disease severity, stressful life events, and clinical maladjustment were not significant predictors of routine service use
Modi, 2009[169]	Barriers and facilitators to adherence to treatment and routine care	Caregivers and adolescent pts Ohio, USA	102*	Forgetting, loss of medication, discomfort, treatment pain, taste aversions, side effects, embarrass-ment	Reminders, peer support, flavor supplements, physician encouragement, use of pills	NR	Caregiver reminders were identified by both caregivers and adolescents as the primary facilitators for pain management, oral antibiotics, chelation therapy, and vitamin and mineral supplements. In addition, support from peers was identified as the primary strategy to facilitate exercise. Caregivers identified several unique facilitators including flavor supplements for hydration, physicians encouraging chelation therapy, and use of pills compared to liquids to assist in hydroxyurea adherence
Newland, 2008[170]	Factors influencing independence in adolescents with SCD	Patients (children, young adults) USA	74	Good family relationships	Less knowledge about the disease, poorer family relationships, & more severe disease		The prediction model was statistically significant but accounted for only 25% of the variance for independence. According to the model, adolescents with SCD that have less knowledge about their disease, poorer family relationships, and more severe disease will be more independent

Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Pejaver, 1997[171]	Patient adherence to prophylactic antibiotics Family report, presence of penicillin in urine	Patients (Children/ Caregivers) Saudi Arabia (armed forces hospital)	41	NR	NR	Patient/ caregiver knowledge, patient age, patient sex, # of children in family, years on therapy, # of inpatient admissions	One quarter (24%) of parents demonstrated good knowledge of the reasons and need for penicillin prophylaxis, however knowledge was not associated with compliance levels in this study.
Pence, 2007[172]	Patient use of pain medication Patient report, family report	Patients (Children/ Caregivers) North Carolina, USA	27	NR	Dispositional optimism	Patient age, patient sex, parent education	For adolescent patients with SCD, pain severity was positively associated with opioid use such that high pain predicted higher use ($p < 0.001$), and pain severity uniquely accounted for the largest proportion of the variance in opioid use (partial r-squared = 0.19). Dispositional optimism was found to moderate the relationship between pain severity and use of opioids ($p < 0.05$). Specifically, at medium and high levels of optimism, pain severity was positively associated with opioid use. At low levels of optimism, pain severity was not associated with opioid use. At low levels of optimism, an intermediate level of opioids was used consistently regardless of whether pain severity was low or high. Additionally, maternal education was found to be marginally associated with adolescent opioid use ($p = 0.08$). Higher maternal education predicted more opioid use, while lower maternal education predicted more non-opioid use.
Shankar, 2008[173]	The impact of proximity to comprehensive SCD center on utilization of healthcare services	Patients (children) USA	1214			Proximity to a comprehensive sickle cell center	The cohort consisted of 1,214 children with 6,393 person-years of follow-up. Fifty-six percent of patients resided in the region with the CSCC. This region had the highest overall rates of hospitalization for all children ($P < 0.001$), while ED and outpatient visits were higher in other areas. The death rates ranged from 1.8 to 4.3 per 1,000 person-years in the four regions and did not represent statistically significant differences

Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Sox, 2003[174]	Receipt of prophylactic antibiotics Administrative data	Patients (Children/ Caregivers) Tennessee, Washington State, USA	261	NR	Private insurance, hospital visits	Patient sex, patient age, urban residence, cost-sharing, non-preventive outpatient care visits	Publicly insured children may receive an inadequate amount of prophylactic antibiotics against pneumococcal infections, as the children in this sample were dispensed an average of only 148.4 days of coverage out of a 365 day period (SD: 121.4, median:114, IQR 39 - 247). The number of outpatient visits for preventive care and the number of emergency department visits experienced by children were significantly associated with increased provision of prophylactic antibiotics. Each visit for preventive care was associated with 12 additional days of prophylactic antibiotic coverage (95%CI 2.3 - 21.7). Each emergency department visit was associated with 10 additional days of coverage (95% CI 1.2 - 18.8).
Teach, 1998[175]	Patient adherence to prophylactic antibiotics Patient report, family report, biologic outcome (urine assay)	Patients (Children/ Caregivers) Buffalo, NY, USA	123	NR	Private insurance, younger patient age	Patient sex, SCD type	Measured compliance was significantly greater in patients <5 years of age than in those >5 (64% vs. 34%, p = 0.004). Patients with private insurance (p = 0.02) had better measured compliance than patients with public insurance. Sex, type of hemoglobinopathy, recruitment site (ED vs. clinic), and chief complaint in ED (fever vs. VOC) were not significantly associated with measured compliance.
Telfair, 2003[176]	Use of routine health services Patient report, administrative data	Patients (Adults and Children/ Caregivers) Alabama, USA	662	NR	Rural geographic region	Community socioeconomic distress, physical functioning, # of medical problems, distance to a clinic	In bivariate analyses, patients with SCD living in rural areas had lower utilization of comprehensive sickle cell services than patients living in urban areas (significance not reported). However, utilization of comprehensive sickle cell services is predicted to be higher for SCD patients in rural areas compared to those in urban areas after adjustment for distance to a clinic, community socioeconomic distress, physical functioning, and a medical problem index (p = 0.003). While the model results suggested that utilization of services increased with increasing socioeconomic distress, the p-value for the result (p = 0.011) did not reach the author's threshold for statistical significance.

Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Thornburg, 2010[57]	Association between treatment adherence and HbF %	Patients (children), care givers. Durham, NC, USA	75	Clinic visits, prescription refills,	Visual analog scale, Morisky score, medical provider report	Age, length of treatment	Good adherence was estimated at 82% with visual analog scale, 84% with Morisky score, 85% with medical provider report, 77% with clinic visits, and 49% on the basis of pharmacy refills. Increase in HbF was moderately associated with good adherence as measured with the parent/proxy Morisky score r = -0.39; 95% CI, -0.58–0.17; P < .01) and prescription refills (r = 0.39; 95% CI, 0.16–0.57; P < .01)
Thornburg, 2010[177]	Adherence to medication and study visits and to evaluate socioeconomic factors influencing measurement of adherence	Patients (children), care givers USA	191		Allowing the families to have flexible scheduling options within the clinic, recognizing warning signs such as conflicts between family members about study participation	Socioeconomic factors (higher education level of the primary caregiver and household income)	MedAd (median study medication) data were available on 153 of the 191 subjects who started randomized study medication. MedAd was 101.7% of volume prescribed, with 88.9% of subjects taking at least 80% of doses. VAd (mean visit adherence) data were available on 185 of the 191 subjects who started randomized study medication. VAd was 97.3%, with 82.2% of subjects having no missed visits. During dose titration, subjects had on average 12.9% higher medication adherence than subjects who were on a stable dose and had less frequent study visits. MedAd and VAd were not significantly associated with SES.
Treadwell, 2005[178]	Patient adherence to chelation therapy Patient or caregiver report, physical examination, administrative records	Patients (Children, Caregivers) California, USA	15	Family stress	Child-parent shares responsibility	Convenience of the regimen, behavioral/ psychological adjustment, patient/ caregiver knowledge, satisfaction with regimen, child cognitive disability	The developmentally appropriate sharing of responsibilities for chelation therapy between parents and their children with SCD contributes to better adherence to home deferoxamine administration ($p < 0.05$). Low family stress was marginally related to better adherence ($p = 0.07$). There was no difference between the most and least adherent group in the perception of the inconvenience of the deferoxamine regimen (significance not shown). The child's behavioral and psychological adjustment was not associated with adherence (significance not shown). The primary hypothesis, that greater child cognitive disability would be a risk factor for nonadherence, was not supported by the data (significance not shown).

Table 19. Barriers and Facilitators (Patient, Provider, and Societal) Shown To Be Associated With Treatment for Patients With Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Witherspoon, 2006[179]	Patient adherence to prophylactic antibiotics Provider report, family report, administrative data	Patients (Children/ Caregivers) USA	30	NR	Caregiver knowledge, intent to adhere, perceived benefits, family employment	NR	Based on pharmacy records, one-third of caregivers had poor (14-30 days/month not 'covered' with antibiotic) and one-third had less than optimal (2-7 days/ month 'uncovered' with antibiotics) levels of adherence to penicillin prophylaxis. Caregiver knowledge of infection and intent to adhere positively predict adherence. Caregivers with better adherence had more knowledge of infection, greater intent to adhere or greater belief in the importance of the medication ($p < 0.05$), and reported fewer barriers to adherence ($p < 0.01$). Families with better adherence rates were more likely to be employed ($p < 0.01$), and reported fewer barriers to adherence ($p < 0.05$).
Wojciechowski, 2002[180]	Transition to adult care Patient report, provider report	Patients (Adults and Children/ Caregivers) Unknown	18	NR	Self-efficacy, female sex	Receipt of preparation for the transfer to adult care	In this study of adolescents and young adults making the transition to adult-centered care, patients with greater SCD self-efficacy kept a higher percentage of their care appointments ($p < 0.05$ using Spearman rho test). Females exhibited better compliance with medical regimens than did males as indicated by higher scores on a scale assessing compliance. There was no significant association between receipt of preparation for the transfer to adult-centered care and compliance with medical regimens.
Wurst, 2004[181]	Provider provision of prophylactc antibiotics/ Provider report	Physicians (hematologists, heme/onc, pediatricians)/ NC, USA	142	Academic medical center setting	Provider knowledge, provider specialty	Provider years in practice, provider gender	Pediatricians were more likely than hematologists to answer correctly 5 or 6 out of 6 questions on SCD antibiotics guidelines ($p < 0.001$). Pediatricians were significantly more likely than hematologists to be 100% adherent in prescribing antibiotics prophylaxis ($p = 0.001$). Physician knowledge of antibiotic prophylaxis prescribing guidelines was associated with better physician adherence to prescribing antibiotics ($p = 0.031$). Physicians in a medical school or university setting were significantly less likely than physicians in other settings to be 100% adherent ($p = 0.033$).

CI = confidence interval; ED = emergency department; HBM = Health Belief Model; HRQOL = health-related quality of life; HU = hydroxyurea; IQR = interquartile range; NR = not reported; SCD = sickle cell disease; SD = standard deviation; VOC = vaso-occlusive crisis, NHLBI: National Heart, Lung and Blood Institute.
* 71 care givers, 31 patients.

Table 20. Summary of Barriers and Facilitators

Subgroup	Factor	Facilitator	Neutral	Barrier
Health care provider	Knowledge and experience	2	1	
	Attitude	2	1	1
	Female gender	1	1	
	Concerns about HU harms			1
	Lack of time to offer counseling			1
Care givers	Knowledge & education	4	3	1
	Poor socioeconomic status	1	3	3
	Family support	3	1	1
	Perceived safety & efficacy	2		
	Frequency of hospital visits	1	1	2
Patients	Peer activities			1
	Prescription refills			1
	Appointment reminders	2		
	More children at home		1	1
	More adults at home	1		
	Young age	1	4	
	Gender		3	
	Disease severity	1	2	
	Forgetting			1
	Loss of medication			1
	Rural region	2	1	
System	Private insurance	2		
	Distance to clinic		3	

Table 21. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Acharya, 2009[66]	Quantitative survey	Patients' parents, care givers	53	Misinformation about what it means to be a carrier and its health and reproductive implications	There was significant misunderstanding about sickle cell inheritance (mean score, 68%), but parents who have a child with SCD have better knowledge compared to those without a child with SCD (78% vs 58%, p = .002). Respondents perceive minimal stigma associated with SCT. Unless there is an affected proband, individuals with SCT rarely receive counseling or education outside of the family
Alleyne, 1995[182]	Qualitative: in-depth semi-structured individual and group interviews	Nurses (inpatient), patients (adults) UK	20 †	Negative provider attitudes, patient race	All 10 patients and 4 nurses expressed dissatisfaction with pain management. Patients (7) reported they had to demand painkillers and wait at least 30 minutes. Patients (8) believed the nurses doubt the genuine nature of the pain, all patients reported lack of involvement in pain control, and all reported that nurses were not sympathetic to pain, telling them, "you'll have to wait." One patient said, "I've got the feeling that some of them purposely prolong it." One nurse suggested that there might be a link between young black people and drug-taking which caused nursing staff to be suspicious of the patients' request for pethidine. Nurses reported frustration with relying on physician orders for narcotics and 2 nurses reported that patients could not be "trusted to be responsible" with patient-controlled analgesia
Booker, 2006[183]	Qualitative: focus groups	Patients (adults) UK	10	Negative provider attitudes	Participants likened dealing with healthcare professionals to a battle. They felt that they had to work hard to convince the doctors that they were in genuine pain and need of help. Some patients felt so disbelieved that they actively avoided consulting when in crisis, for fear of being perceived as opioid dependent. Many patients felt that doctors did not have sufficient knowledge of sickle cell disease to make valid treatment decisions
Burnes, 2008[184]	Qualitative survey	Care givers (mother) Canada	10	Lack of research and resources for SCD, lack of knowledge and skills about SCD, racism, fear for children safety	Mothers commonly reported several daily coping challenges: fear of their children's death, separation anxiety, loss of control over life, helplessness, and loneliness/isolation. SCD stigma interacted with racism, contributed to social isolation, and prevented families from organizing as a group. They also expressed frustration at lack of public awareness of the disease and its stigma. Lack of research. Knowledge and skills were the main health care system related barriers
Butler, 1993[185]	Qualitative: authors' reports of themes that arose in a SCD support group that included medical residents	Patients (adults) USA	24	Negative provider attitudes	During their lives, each member of the group had experienced many negative interactions with health care providers, including routinely being treated with suspicion and distrust. Patients expressed extreme frustration in attempting to convince health professionals of their distress

Table 21. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Chestnut, 1994[186]	Qualitative: structured interview and service perception test (spt) in which subjects had to choose patients (via pictures) who they felt would receive better care	Nurses, doctors (hematologists), medical staff, patients (children/ caregivers) USA	29 §	Patient race, patient sex, patient age	Family respondents perceived that younger children get the best care (regardless of gender or race), that whites get better service than blacks (regardless of age or gender), and that females get better care than males. Medical staff also perceived that children, whites, and females get better care than adults, blacks, and males
Crosby, 2009[162]	Qualitative survey, using two phases, one is a focus group and the other is an individual semi-structured interview	Patients' parent, care givers Midwest, USA	45	Competing activities involving school or peers; birthdays, homework	Adolescents identified competing activities, health status, patient-provider relationships, adverse clinic experiences, and forgetting as barriers to clinic attendance. Calendars/reminders and parent reminders were the most commonly reported strategies to facilitate clinic attendance. Adolescents also reported the need for flexible scheduling and improved patient-provider communication
Harris, 1998[187]	Qualitative: standardized, structured open-ended interviews	Patients (adults) UK	27	Negative provider attitudes	Study participants were satisfied with pain relief (78%), but 30% stated pain control would be improved with more prompt administration of meds. Overall hospital service was reported as "satisfactory to good" by 63%, but 44% made a complaint about the staff's negative attitude to people with SCD, 26% felt staff generally lacked knowledge and understanding of SCD and pain crises, 22% said staff did not believe or appreciate that they were in pain ("they treat us like liars") and 19% said nurses were slow to give analgesia and attended to other "less urgent" tasks (such as "pillows")
Labbe, 2005[166]	Quantitative: questionnaires	Doctors Alabama	109	Negative provider attitudes, inadequate pain assessment tools	Physicians hold a number of beliefs and attitudes which may affect the quality of pain management delivered to patients with SCD. While the patient's self-report of pain was the tool most commonly used by physicians in assessing the severity of pain (92% of respondents), 86% of the physicians "somewhat disagreed to disagreed" that the most reliable indicator of the existence and intensity of pain is the patient's self-report. Physiological and behavioral measures were also commonly cited tools used to assess pain severity. The top 5 barriers to optimal pain management in SCD as reported by these physicians were lack of psychological support from patient's family and the medical profession, fear that the patient is a drug abuser, reluctance to prescribe opioids, disbelief in patient's report of pain severity, and inadequate pain assessment tools

Table 21. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Lanzkron, 2008[167]	Quantitative: 45-item questionnaire sent to members of the Sickle Cell Adult Provider Network (SCAPN).	Physicians, nurse practitioners, physician assistants, and other providers Location Unknown	48	Provider concerns to prescribe HU, lack of time/resources to adequately explain the risks/benefits,	Providers were concerned about (Patient will not be compliant with needed blood tests 74% Patient will not use appropriate contraception 63% Patient will not be compliant with hydroxyurea 50% Patient does not have enough info about hydroxyurea 43% Patient's anticipation of side effects 35% Patient is too young 18% Concern over carcinogenic potential 17% Provider lacks the time/resources to adequately explain the risks and benefits of hydroxyurea 13% Concern over cost 11% Patient is too old 2%)
Maxwell, 1999[188]	Qualitative: 18 semistructured interviews with 15 individuals and 8 focus groups	Patients (adults) London, UK	57	Negative provider attitudes	In focus groups, patients reported negative experiences with hospital care. These were characterized by mistrust (being suspected by health professionals of exaggerating pain), stigmatization (treated differently from other inpatients--"drug addicts"), control (health professionals exerted control and failed to involve patients in decision-making), neglect (of personal care, monitoring of vital signs, and psychosocial support due to understaffing or low priority). A minority of patients responded to unsatisfactory care by self-discharging from one hospital and going to another
Modi, 2009[169]	Quantitative: questionnaire about HU and routine care barriers and facilitators	Caregivers, and adolescent pts Ohio, USA	102 ++	Forgetting, loss of medication, discomfort, treatment pain, taste aversions, side effects, embarrassment	Forgetting to take medication or loss of medication was the primary barrier identified by both caregivers and adolescents for pain management, hydroxyurea, and vitamin and mineral supplements, whereas fatigue was the primary barrier for exercise. Both caregivers and adolescents endorsed treatment pain or discomfort as barriers to chelation therapy and exercise, and taste aversions or side effects (e.g., nausea, racing heart) as barriers to pain medication and oral antibiotics. However, adolescents also uniquely identified side effects as barriers to transfusions (e.g., fever, chills), hydration (e.g., bloating), and vitamin and mineral supplements (e.g., constipation), along with taste aversions for the latter two treatments. Adolescents also reported questioning medication efficacy and a desire to be "normal" as barriers to oral antibiotics. In contrast, caregivers uniquely reported difficulty incorporating transfusions, hydration, and vitamin and mineral supplements into daily life, worry and anxiety about receiving transfusions, and embarrassment of doing chelation therapy (e.g., subcutaneous or intravenous injections) in front of others (e.g., friends, family) at home
Murray, 1988[189]	Quantitative: questionnaires	Patients (adults) UK	102	Negative provider attitudes	Of the 88 patients who went to the hospital for care, 18 thought they were seen quickly, 33 thought the delay was too long, 17 were concerned about side effects of medications, 40 said pain relief "was there when needed", but only 23 routinely received analgesics on demand, and 57 patients thought staff did not appreciate the amount of pain they were having

Table 21. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Pack-Mabien, 2001[190]	Quantitative: questionnaires (written 31-item multiple choice survey about nurses' attitudes and perceived barriers to opioid pain management of sickle cell patient pain episodes)	Nurses USA	200	Negative provider attitudes, lack of provider knowledge, lack of time, inadequate pain assessment tools	Many nurses believed that drug addiction frequently develops in sickle cell patients (63%) and reported (49%) that they did not have broad knowledge of sickle cell disease. 59% reported Inadequate pain assessment tools were reported by 59% as the greatest barrier in the management of pain episodes. Lack of time for psychological support of patients (58%), nurse reluctance to provide opioids (37%), a narrow range of available analgesics (37%), physicians' reluctance to prescribe opioids (33%), and the belief that most sickle cell patients are drug addicts (32%) also reported barriers
Pejaver, 1997[171]	Quantitative: questionnaires	Patients (children/ caregivers) Saudi Arabia	41	Forgetting, disliking taste, concern about side effects	Common reasons given for non-compliance with penicillin were forgetting to give the medicine, forgetting to renew the supply of medicine, the child not liking the medicine, and the feeling that daily medication could have ill effects
Rouse, 2004[191]	Qualitative: observations made while performing anthropological research on two children's hospitals	Nurses, doctors, patients (adults) California and Pennsylvania, USA	NR	Negative provider attitudes	In the wards, residents and nurses dismissed patients' demands for pain relief as drug addiction, malingering, or manipulation. Furthermore, several staff members stated that "patients were being denied proper medical care, unfairly accused of drug use or criminal behavior, transferred to adult care clinics at an early age, and generally treated with less respect than the cancer patients who occupied the same floor in the hospital." With few exceptions, the nurses' perceptions of their sickle cell patients were overwhelmingly negative. During one session, it was revealed that while nurses believe cancer patients' self-reporting of pain, they generally believed that their sickle cell patients inflated their level of pain. One nurse said, "One of the problems with sickle patients, I believe, is that healthcare professionals make a connection between African-Americans using drugs and existing stereotypes; and that is coupled with health care professionals' lack of knowledge about sickle cell disease."
Shelley, 1994[192]	Qualitative: phone interviews	Patients (adults, SCD self-help group leaders) USA	11	Negative provider attitudes, lack of provider knowledge	Patients perceived problems in health care services delivery. Inadequate staff training and high turnover in the ED, health providers' fears of drug addiction, negative attitudes of physicians to patients, delays in ED, unfamiliarity of staff with SCD, routine accusations of drug-seeking, insensitivity of physicians to patients' pain, and negative reactions by physicians to patient attempts to be involved in the course of their own care were all reported. Most group leaders cited the unfamiliarity of ER staff with SCD as a factor which contributes to delays in treatment of VOCs. Several group leaders also cited provider insensitivity to patients' pain as a problem. Almost half of group leaders reported negative reactions on the part of some physicians to patients, including ignoring a patient, blunt remarks about the doctor's amount of knowledge vs. the 'lay' patient. Group leaders reported that these sorts of incidents keep some SCD patients from the ED, even when they are in pain

Table 21. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Strickland, 2001[193]	Qualitative: focus groups	Patients (adults), family members USA	21‡	Negative provider attitudes	In focus group sessions, adults with SCD stated the belief that nurses would not give them pain medications when needed because the nurses believed that persons with SCD are addicts. Adults with SCD also stated the belief that some medical providers are intimidated when patients demonstrate knowledge about their disease or their pain control
Telfair, 1998[194]	Quantitative: questionnaires (providers were asked to agree or disagree with 3 questions about (1) quality of health care provided to persons with SCD, (2) decisions about the administration of pain medication, (3) quality of interpersonal relationships between health care providers and patients)	Nurses, doctors, physician assistants, social workers USA	227	Patient race	Providers generally disagreed that race influences delivery of health care to individuals with SCD (52% disagree that quality is influenced, 77% disagree that pain medication decisions are influenced, 52% disagree that quality of interpersonal relationships are influenced). In bivariate analyses, 76% African-American vs. 35% Caucasians ($p < 0.00$) agreed that race is an influence on quality, and 30-54% females vs. 12-37% males ($p < 0.01$) agreed with all three statements regarding race as an influence on health care provision. More urban providers (26%) vs. rural providers (11%) agree that race influences pain medication decisions ($p < 0.02$). In multivariate analysis, AA provider race was associated with all three questions ($p < 0.01$): quality (or 5.6, 95% CI: 2.80,11.22); pain medication decisions (or 3.1, 95%CI: 1.54,6.19); quality of relationships (or 3.9, 95%CI: 2.02,7.38)
Thornburg, 2010[57]	Quantitative: Single institution cross-sectional prospective study. Caregivers were given a questionnaire to fill out on factors that may affect adherence	Patients (children) Durham, NC, USA	75	Clinic visits, prescription refills	The proportion of subjects with good adherence was $75% with 4 of 5 measures. Although there was significant increase in HbF, there was variability in response, which was partially explained by lack of adherence on the basis of pharmacy prescription refills and Modified Morisky Score

Table 21. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Tucker, 1995[195]	Qualitative: focus groups	Patients (adults) California, USA	NR	Negative provider attitudes, lack of provider knowledge	In 12 support group sessions of 2-8 patients each, patients all agreed on two major problem areas: (1) obtaining appropriate medical care in the ER (time to admission, feeling "forgotten", would delay hospital visits out of "dread") and (2) difficulty relating to members of the health care team (poor communication, "providers did not believe them", pain medication "not strong enough", discharged "too soon", being told "the pain is all in your head." Also, patients noted lack of knowledge by providers, felt "they are encouraged to 'act out' the pain in order to be taken seriously and medicated appropriately. Several group members said that "they would do everything possible" to keep from coming to the hospital because they dreaded the admission procedures
Vichinsky, 1999[196]	Quantitative: questionnaires (directors and associates of SCD centers were asked to comment on provision of care by community physicians using a survey tool developed for this study)	Directors and associates of sickle cell disease centers USA, Canada	21	Lack of provider knowledge	In most categories, over 90% of respondents stated that care provided by physicians from their centers complied with NIH guidelines, as compared to many fewer (50% or less) who reported that care by community physicians complied with NIH guidelines in all categories except care related to infection (60%) and contraception and pregnancy care (59%). Most respondents (72%) believed that lack of knowledge or training was the reason that community physicians failed to follow NIH guidelines
Walters, 1996[197]	Quantitative: questionnaires (bone marrow consortium participants were asked to report on barriers at their institutions)	Physicians USA (multi-center study)	315	Lack of donor, lack of financial/ psychosocial support, parental refusal, physician refusal, history of noncompliance	315 out of 4,848 patients from 22 centers were reported to be eligible for bone marrow transplantation (BMT). Of the 315, 187 did not undergo HLA typing. The reasons for this included lack of HLA matching donor (76/187), lack of support (33/187), parental refusal (30/187), and physician refusal (13/187). Among those who had an HLA-identical donor (44), parental refusal was the most frequent reason for not performing a BMT
Waters, 1995[198]	Mixed: questionnaires (self-administered in presence of research coordinator) with qualitative analysis of open-ended responses.	Nurses (inpatient), patients (adults) UK	26*	Negative provider attitudes, lack of provider knowledge, lack of time	Factors reported by the subset of 13 nurses who felt they could better relieve sickle cell pain were time (4/13), lack of knowledge of narcotic analgesia (4/13), fears of overdosing and addiction (4/13), and lack of experience with sickle cell patients (2/13). Most patients (7/9) felt less in control of pain while in the hospital as compared to at home and wanted to be more involved in management of pain while on the ward. All patients stated they had to ask if they wanted more analgesia although the "majority" of nurses said they assessed pain continually. The majority of patients considered nurses' knowledge of sickle cell crisis and sympathy towards them as a patient group to be poor. Evidence of unsatisfactory pain management evidenced by comment from patient: ". . . You can just tell sometimes that they don't agree with having to give you the injection"

Table 21. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Witherspoon, 2006[179]	Quantitative: questionnaires	Patients (children/ caregivers) USA	30	Caregiver being busy, forgetting to administer medications, child falling asleep, running out of medication	Commonly reported barriers to adherence were: the caregiver being busy (26.7%), forgetting to administer the medication (23%), the child falling asleep (20%), and running out of medication (16.7%)
Zumberg, 2005[199]	Quantitative: questionnaires (27item, 4-page self-administered questionnaire)	Doctors (hematologists) Florida, North Carolina, USA	184	Patient compliance, lack of contraception, patient anticipation of side effects, patient age, provider concern about side effects, provider doubting effectiveness, cost	There were differences in HU prescribing between community and academic physicians showed differences in HU prescribing in the treatment of ACS (43% vs. 70%, p = 0.006), stroke (40% vs. 60%, p = 0.04), and pulmonary hypertension (7% vs. 23%, p = 0.008). Community physicians less frequently monitored compliance by pill count (7% vs. 20% in academic physicians, p = 0.03) and MCV measurements (36% vs. 90%, p < 0.0001). Concerns that were identified as "important" or "very important" barriers to the use of HU were patient compliance (90%), lack of contraception (79%), patients' anticipation of side effects (82%), patient's age (50%), cost (59%), concern about carcinogenic potential (40%) and doubting effectiveness (40%).

* 9 patients and 17 nurses

† 10 nurses and 10 patients

‡ 10 patients and 11 family members

§ 22 patients and 7 staff

AA = African American; ACS = acute chest syndrome; BMT = bone marrow transplant; CI = confidence interval; ED = emergency department; ER = emergency room; HU = hydroxyurea; MCV = mean corpuscular volumes; NIH = National Institutes of Health; NR = not reported; OR = odds ratio; SCD = sickle cell disease; SPT = service perception test; VOC = vaso-occlusive crisis.

Table 22. Description of Interventions To Improve Patient Care in Sickle Cell Disease

Author, year	Study design	Study population Study location	N	Intervention objective Main intervention components	Intervention description
Benjamin, 2000[200]	CCT, Pre-Post	Nurses, doctors, social workers, patients Bronx, NY, USA	144	To decrease the load of the ED and to study the value of a dedicated facility with knowledgeable staff applying principle-based individualized care. **Establishment of Day Hospital**	Establishment of a Day Hospital with comprehensive assessment and treatment protocol (assessment and initial treatment within 15-20 minutes of arrival followed by assessment with established instruments every 30 minutes). Protocol included assessment, individualized drug management, medication titration to relief, maintenance of relief, use of combination drugs to enhance efficacy/toxicity ratio, monitoring of adverse events, identifying and treating precipitating factors, and appropriate disposition
Berkovitch, 1998[201]	RCT	Patients (children/caregivers) Toronto, Canada	23	To establish a simple method of improving compliance with antibiotics in children with SCD. **Education and follow-up by medical professionals**	Intervention subjects attended slide show (describing pathophysiology of SCD, risk of infections, importance of antibiotics), received stickers and a calendar to document compliance, and got a weekly phone call from social worker (asking questions about treatment, general health, other meds, family problems). Control and intervention subjects were invited to clinics every 8 weeks, where meds were dispensed and compliance evaluated. At end of 6 months, parents in both groups completed a questionnaire to determine knowledge and understanding of SCD
Brookoff, 1992[202]	Pre-post	Nurses, doctors, patients (adults) Philadelphia, PA, USA	50/ yr	To determine if providing adequate pain control (using continuous morphine infusions and sustained courses of orally administered controlled-release morphine) for the treatment of SCD in adults can decrease hospital visits and admissions for sickle cell pain. **Clinical protocol/pathway**	Intravenous and oral controlled-release morphine was used instead of intramuscular meperidone and short-acting opiods in treatment of pain
Co, 2003[203]	Pre-post, CCT	Patients (children/caregivers) Baltimore, MD, USA	369	To improve the care for pediatric SC VOCs **Clinical protocol/pathway**	Clinical pathway for the treatment of children aged 2 – 19 years with VOC requiring hospitalization. Use of IV fluids, incentive spirometry, and pain service consultation were main check points for the pathway

Table 22. Description of Interventions To Improve Patient Care in Sickle Cell Disease (continued)

Author, year	Study design	Study population Study location	N	Intervention objective Main intervention components	Intervention description
Cooper, 2000[204]	CCT, Pre-post	Nurses, doctors Cleveland, OH, USA	67	1) Develop individualized pain management protocols 2) Discourage the use of meperedine in favor of morphine, hydromorphone, and levorphanol 3) To use buprenorphine for patients with known or suspected narcotic dependence. **Clinical protocol/pathway**	The intervention was developed by establishing consensus concerning guidelines for care of SCD patients, and then educating physicians, nurses and house staff on new guidelines via Grand Rounds, conferences, medical management conferences, informal presentations, audiotapes and mailings. Patients were identified via admitting diagnosis and a care manager or physician made recommendations based on guidelines. Individualized care plans were constructed for "frequently admitted" sickle cell patients and were entered into mainframe for access by all physicians
Day, 1997[205]	Pre-post	Nurses, doctors, patients UK	18	To retrospectively audit admissions of SCD patients to identify problems with pain management and look for improvements after the care guidelines were introduced to department. **Audit and Feedback**	One nurse audited 10 admissions prior to implementation and 8 admissions after implementation to evaluate time to receive analgesia, what was prescribed, dose and method of administration, whether the pain management team was called, whether patient-controlled analgesia was used, and to which ward patient admitted. Data from the initial audit were shared with providers
Fertleman, 1997[206]	Pre-post	Nurses, doctors, patients (children/caregivers) London, UK	72	To evaluate the efficacy of fast track system in which children with SCD are directly admitted to the ward after a telephone call from parent, assessed immediately, and given intramuscular pethidine if indicated (dose pre-prescribed). **Establishment of fast track admission procedures**	Fast track system in which children with SCD are directly admitted to the ward after a telephone call from parent, assessed immediately, and given a (pre-prescribed, documented) dose of intramuscular pethidine if indicated. Time to treatment pre- (1994) and post-implementation (1995) were compared. Parents (25) whose children had used both systems completed questionnaires about both

Table 22. Description of Interventions To Improve Patient Care in Sickle Cell Disease (continued)

Author, year	Study design	Study population Study location	N	Intervention objective Main intervention components	Intervention description
Jamison, 2002[207]	Pre-post	Nurses, doctors, patients Greensboro, NC, USA	204	1) To improve overall satisfaction of patients with SCD who were cared for at the study hospital (tertiary care hospital in the southeast) 2) To reduce the length of stay of patients with SCD 3) To reduce the costs associated with hospital treatment of patients with SCD. **Clinical protocol/pathway with sensitivity training**	Intervention included staff education (sensitivity training, information about SCD, pain management and other treatment interventions), nurse education about complementary therapies and other diversional activities, and a protocol to be used which included standing orders to evaluate and treat crises. Patients who did not have adequate control within 8 hours and who were moved to inpatient area were all admitted to oncology ward rather than diverse departments. Patient education materials, safety guidelines for admission, identification cards and discharge instructions (including document with education and resources) were developed
Ketchen, 2006[208]	RCT	Patients (children/caregivers) US, Canada	37	To evaluate the efficacy of the home version of Starbright World, a Web-based computer network designed to connect chronically ill children, on increasing knowledge of SCD, increasing engagement in health-promoting activities, and improving psychosocial functioning. **Education and peer support**	Access to Starbright World with weekly assignments (educational and social activities and those that encouraged child-parent participation). Staff member called caregiver weekly
LaVista, 2009[209]	Qualitative observational study	Patients, physicians USA	58	Develop and evaluate an intervention to empower patients and their families to discuss with their physician the risks and benefits of HU **Educational video**	Video content was developed based on gaps in patient knowledge discovered during patient interviews and observed by physicians caring for patients with SCD. A 15-minute DVD entitled “Hydroxyurea: Is it Your Hope for Better Days?” included patients discussing experiences with HU, and SCD experts discussing risks and benefits of HU and potential questions for patients to ask physicians
Mitchell, 2002[210]	Pre-post	Nurses, doctors, social workers, patients Philadelphia, PA, USA	27	To improve the consistency and quality of care for patients with SCD having a VOC at a 200bed community hospital. **Clinical protocol/pathway**	Implementation of new mandatory pain management protocol emphasizing aggressive pain management in the ED (using morphine sulfate or dilaudid rather than meperedine), admission to medical-surgical unit if crisis not resolved in 8 hours, and continued PCA, IV fluids, and oxygen. Physicians and nurses received in-service training related to the new protocol. One case manager was also assigned to coordinate all care

Table 22. Description of Interventions To Improve Patient Care in Sickle Cell Disease (continued)

Author, year	Study design	Study population Study location	N	Intervention objective Main intervention components	Intervention description
Patik, 2006[211]	Pre-post	Patients (children/caregivers) Pittsburgh, PA	202	To determine the feasibility and acceptance of the intervention for families with a child with SCD and the impact of the intervention on adherence to comprehensive care. **Education and non-medical follow up support**	Telephone-delivered structured follow-up, support and education by non-medical personnel (graduate student researcher). The semi-structured script included questions related to patient's well-being and health-related behaviors and was administered at 3-month intervals from the last contact.
Thornburg, 2010[177]	Prospective RCT	Patients (children), care givers USA	191	Increase adherence **Efforts by study personnel to reinforce the importance of adherence and implementing creative solutions to overcome barriers**	NR
Treadwell, 2001[212]	Pre-post	Patients (children/caregivers) California	11	To increase patients' knowledge of the disease and treatment regimen within a setting that encouraged and assisted peer interactions, and ultimately to enhance treatment adherence. **Education and peer support**	Desferel Day Camp - provided peer support and education for 4 days each summer.
Treadwell, 2002[213]	Pre-post	Hospital staff, patients (children/caregivers) USA	235	To implement developmentally appropriate pain assessment guidelines for pediatric inpatients **Clinical protocol/pathway**	Staff was educated on the use of pediatric pain assessment tools and a standardized pain assessment protocol was put into practice.

CCT = clinically controlled trial; ED = Emergency department; IV = intravenous; LOS = length of stay; PCA = patient controlled analgesia; RCT = randomized controlled trial. SCD = sickle cell disease; VOC = vaso-occlusive crisis.

Table 23. Results of Interventions To Improve Patient Care in Sickle Cell Disease

Author, year	Primary outcome (directness)	Outcome measurement	Primary results	Summary
Benjamin, 2000[214]	Utilization, pain management quality (direct)	Administrative data were used.	Walk-in DH patients discharged to home increased from 70% in first 2 years to 90-94% in last 3 years. The average length of stay in DH was 4.5 hours (range 2 to 7 hours) vs.13 hours (range 11 minutes to 90 hours) in the ED. Treatment time in the ED before transfer to DH was 16 hours in year 1 vs. 8 hours in year 5. Visits resulting in admission were lower for DH patients (8%) vs. ED patients (51%). Admission rate in patients with uncomplicated pain was 776/1818 (42.7%) ED patients vs. 168/2033 (8.3%) DH patients. The use of meperidine decreased from 90% in year 1 to 63% in year 5, while the use of hydromorphone increased from 3% (Year 1) to 33% (Year 5). There were no p-values reported	Potential improve-ment
Berkovitch, 1998[201]	Patient adherence (direct)	Family reports, administrative data, and medication event monitoring system were used. At 6 months, parents in both groups completed questionnaire.	Compliance at 2-4 months was 79.0% (±31.4%) in intervention group vs. 66.0 (±20.2%) in control group (p = 0.297). Compliance at 4-6 months was 82.0 (±34.7%) in intervention group vs. 65.8 (±25.3) in control group (p = 0.366). There were no significant differences in admission rates, or in measures of parent knowledge of SCD	No improve-ment
Brookoff, 1992[202]	Utilization (indirect)	Administrative data and patient reports were used. Data on admissions and duration of hospital stay were collected for patients with SCD for all admissions from Jan 1 to June 30 in the years 1985 to 1990. ED visit data was collected for Jan 1 to June 30, 1988-1990. The new protocol was implemented in 1989.	Following this intervention, the total number of emergency department visits declined by 67% (426 to 138), the number of admissions declined by 44% (115 to 65), and the duration of hospital stay decreased by 23% (7.12 days to 5.45 days). There were no p-values reported. New protocol "met with strong resistance by a few patients" but this was eased by allowing these patients to "participate in developing their own analgesic plan."	Potential improve-ment
Co, 2003[203]	Pain management quality (direct)	Administrative data (use of IV fluids, incentive spirometry, and pain service consultation) were used.	Of 369 patients, 139 were admitted before the pathway, and 230 were admitted after the pathway. Physicians used the pathway 43% of the time after the pathway became available. Pathway patients were more likely than non-pathway patients to have received IV fluids (OR = 1.15, 95% CI 1.07 -1.23), incentive spirometry (OR = 2.49, 95% CI 2.02-3.07), and pain service consult (OR = 1.33, 95% CI 1.18 -1.50). Pathway patients had longer length of stay (p = 0.01) and time to oral pain medication (p < 0.001) than non-pathway admissions. No difference in readmission rates	Improve-ment
Cooper, 2000[204]	Utilization, costs, pain management quality (direct)	Administrative data were used	Of 58 care-managed admissions (study group) and 9 non-caremanaged admissions (control group), the median unadjusted hospital length of stay was 3.5 days in the study group versus 4 days in the control group (p = 0.54). Costs were $2,920 in study group versus $3,157 in control group (p = 0.32). The use of non-guideline narcotic meperedine decreased from 82% pre-implementation to 18% post-implementation. (p < 0.001)	Improve-ment

Table 23. Results of Interventions To Improve Patient Care in Sickle Cell Disease (continued)

Author, year	Primary outcome (directness)	Outcome measurement	Primary results	Summary
Crosby, 2009[162]	Patient awareness (direct)	Pre-post surveys	Patients expressed a strong desire after viewing the video to learn about potential benefits of HU. Furthermore, the video was useful in heightening the intent of patients to ask their health care providers about HU therapy	Improve-ment
Day, 1997[205]	Pain management quality (direct)	Administrative data were used.	After the intervention, the use of intramuscular pethidine decreased from 8/10 to 0/8 and the use of patient-controlled analgesia with morphine increased from 1/10 to 7/8. The incidence of calling the pain team promptly at admission increased from 1/10 to 8/8. The author reports that the time to see physician was "often. . .not immediate" prior to the intervention, but changed to "all. . . seen by a doctor immediately upon arrival" after the intervention.	Potential improve-ment
Fertleman, 1997[206]	Pain management quality, patient ratings (direct)	Family reports and administrative data were used	Median time to pethidine decreased from 38 min to 5 min ($p < 0.001$). 21 of 25 questionnaires were returned and all parents preferred the fast track system. Parents "added that the ward staff knew more about SCD, knew their children, and did not ask irrelevant questions before giving pethidine"	Improve-ment
Jamison, 2002[207]	Patient ratings, utilization, costs (direct)	Patient reports, administrative data were used	A pain management questionnaire administered to 9 patients at the beginning of implementation and to 10 patients 6 months later showed "marked improvement in the follow-up 6 month survey." Patient satisfaction post questionnaire that asked patients about satisfaction pre and post implementation was administered to 18 patients, and suggested that satisfaction overall improved. There was an overall trend in decreasing LOS post-implementation. Admissions to the ED or inpatient departments decreased >50% post-implementation. There was an 18.5% decrease in inpatient costs and 29.6% decrease in costs of observation stays. There was no significance testing reported in the article	Potential improve-ment
Ketchen, 2006[208]	Health promotion activities, parent-child relationships, child quality of life, child depression (direct)	Patient/family reports were used. Data collection occurred pre-intervention and 2 months post-intervention of SCD	Intervention and control groups did not differ with respect to demographic, disease severity, pre-study computer ownership, or exposure to health education programs. Children in the intervention group had significant improvements in quality of life [child quality of life (lower scores better): pre: 32.70 (17.64) in intervention vs. 35.27 (17.08) in control Post: 29.90 (15.34) in intervention vs. 31.44 (25.05) in control time. Children in intervention group showed improvements in parent-child relationships [pre: 14.50 (6.19) in intervention vs. 17.82 (4.28) in control and post: 16.04 (4.75) in intervention vs. 17.18 (5.00) in control time. There was a non-significant trend towards children in the intervention group having improvements in depression scores. There were no significant differences between intervention and control groups in health promotion activities or child knowledge of SCD	Partial Improve-ment
Mitchell, 2002[210]	Utilization (indirect)	Administrative data were used. Outcomes were measured 6 months before and 6 months after protocol.	There were 235 visits to the ED with 76 admissions (68% treat-andrelease) pre-intervention compared to 188 visits to the ED with 46 admissions (76% treat-and-release) post intervention. The average length of stay decreased from 4.9 days to 3.8 days. The authors report that there were no patient complaints during the intervention and that patients commented that "pain was being managed more efficiently." There was no significance testing reported in the article	Potential improve-ment

Table 23. Results of Interventions To Improve Patient Care in Sickle Cell Disease (continued)

Author, year	Primary outcome (directness)	Outcome measurement	Primary results	Summary
Patik, 2006[211]	Rate of patient non-attendance at clinic for 2 years (direct)	Cross-sectional patient survey prior to the start of the intervention and repeated 18 months later.	147 of the 202 patients (73.6%) were available and willing to talk. 64% of patients requested a service during the phone call (e.g. prescription refill, information, appointment scheduling). The proportion of patients who had not attended clinic for >2 years decreased from 19.7% to 9.9% (p = 0.002) following intervention, and transcranial doppler compliance increased from 34% to 49% (p = 0.05)	Improve-ment
Treadwell, 2001[212]	Patient adherence (direct)	Patient reports were used.	Participation in Desferel Day Camp did not result in increases in measures of patient knowledge, peer support, or adherence to therapy	No improve-ment
Treadwell, 2002[213]	Pain management quality, patient ratings (direct)	Patient report, family report, administrative data	Patients, families, and staff reported increased pain assessment, improved staff responsiveness to patients' pain and greater satisfaction with assessment tools post-intervention (all p-values <0.05). Increased compliance with the assessment guidelines was confirmed by chart audit.	Improve-ment

CI = confidence interval; DH = day hospital; ED = emergency department; IV = intravenous; LOS = length of stay; OR = odds ratio; SCD = sickle cell disease.

Table 24. Outcome Data Stratified by Dosage in Adults

Study label	Study arm (N)	Hb F%*	%F cells*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
MTD: Al-Jam'a, 2002[13]	Post-HU (27) Pre-HU (27)	Post-HU: 25.7 (7.3) median = 25# Pre-HU: 12.6 (5.4)		Post-HU: 10.7 (1.4) median = 10.8# Pre-HU: 9.71 (1.2)		Post-HU: 6,260 (2,580) median 5,600# Pre-HU: 8,990 (3,480)	Pre-HU: 6.5 /yr(2.8)	Post-HU: 0.93 (2.2) Median = 0†; hospital days 5.1 (13.5) median 0# Pre-HU: Hospital days 33.9 (26.1)	
MTD: Charache. 1992[18]	Post-HU (32) Pre-HU (49)	Post-HU: 15 (6) † Pre-HU: 4 (2)	Post-HU: 73 (17) † Pre-HU: 28 (14)	Post-HU: 9.7 (1.8) † Pre-HU: 8.4 (1.4)	Post-HU: 117 (15) † Pre-HU: 94 (8)	Post-HU: 8400 (1400) † Pre-HU: 13,400 (3200)	Post-HU: 1.3 (2) / 6-months [0 - 9]‖ Pre-HU: 4 [020]/6 months		Post-HU: Mean 4.3 kg weight gain†
MTD: Voskaridou, 2010[60]	HU (131) Non HU (199)	HU: 17.4 [0.8-38.3] Non HU: 4.9 [0.8-38.3]		HU: 9.5 [6.3-13] Non HU: 9.1 [5.5-13.6]	HU: 96.8 [79.8 127.2] Non HU: 71.1 [62.8-99.2]		HU: 0.025 (0.026) >95% reduction	HU: 0.041 (0.018)	HU: Some outcome data not reported for non HU arm. Some outcomes were reported per year.

Table 24. Outcome Data Stratified by Dosage in Adults (continued)

Study label	Study arm (N)	Hb F%*	%F cells*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Non MTD: Berthaut, 2008[16]	Before HU (34) During HU (5) After HU (8)								Before HU: Volume of ejaculate 3.08±1.67 ml, Spermatozoa concentration 38.55±43.12 millions/mL, Total sperm count 114.17±124.12 millions, Initial forward motility 28.66±18.38 % of motile, Spermatozoa morphology 21.92±14.63 % of normal, Vitality 59.75±21.61 % of living During HU: Volume of ejaculate 2.68±1.28 ml, Spermatozoa concentration 2.66±3.75 millions/mL, Total sperm count 7.02±10.18 millions, Initial forward motility 30.00±5.77 % of motile, Spermatozoa morphology 34.50±21.92 % of normal, Vitality 52.00±14.23 % of living After HU: Volume of ejaculate 2.99±2.85 ml, Spermatozoa concentration 18.46 ± 26.86 millions/mL, Total sperm count 61.12±107.37 millions, Initial forward motility 29.46±20.13 % of motile, Spermatozoa morphology 19.16±16.3 % of normal, Vitality 44.40±20.12 % of living
Non MTD: Dahoui, 2010[20]	Normal tricuspid regurgitant velocity (58) PHTN (27)								Normal tricuspid regurgitant velocity: Pts on HU had a higher prevalence of PHTN and Hu was not able to stop PHTN from developing in 5 pts
Non MTD: el-Hazmi, 1992[24]	Post-HU (21)	Post-HU: 19.8 (4)†		Post-HU: NR †	Post-HU: NR†	Post-HU: 6,629 (2603) †			Post-HU: P-value relative to baseline

Table 24. Outcome Data Stratified by Dosage in Adults (continued)

Study label	Study arm (N)	Hb F%*	%F cells*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Non MTD: Italia, 2009[2]	Adult HbSS (29) Adults Hb Sßthal (23)	Adult HbSS: 23.1 (5.2) Adults Hb Sßthal: 26.9 (10)	Adult HbSS: 82.7 (8.7) Adults Hb Sßthal: 70.3 (18.2)	Adult HbSS: 10.7 (1.5) Adults Hb Sßthal: 9.8 (1.7)	Adult HbSS: 95.4 (11.8) Adults Hb Sßthal: 77.2 (12)	Adult HbSS: 8 (2) Adults Hb Sßthal: 8.2 (3.3)	Adult HbSS: 0-1/yr: 83% 2-3/yr: 17% Adults Hb Sßthal: 0-1/yr: 87% 2-3/yr: 13%	Adult HbSS: 0: 97% 1-2/yr: 3% Adults Hb Sßthal: None: 100%	
Non MTD: Lefevre, 2008[39]	HU (80) Non HU (39)	HU: NR	NR	NR	NR	NR	NR	NR	HU: 2 presented stroke; 4 patients with a previous history of stroke but only 1 presented a new episode; recurrence rate of stroke was 2.9 for 100 patient-years; incidence of first stroke 0.36 for 100 patient-years Non HU: Velocity increases with age to a max between age 6 to 9
Non MTD: Little, 2006[40]	A: High-risk SCD with HU intolerance (5) B: High-risk SCD with relative renal insufficiency (5) C: Misc (3)	A: High-risk SCD with HU intolerance: 13.5 [3.1-21], up from 5 [1.6-14]	A: High-risk SCD with HU intoler-ance: 47.5 [24-75], up from 22 [13 - 66]	A: High-risk SCD with HU intolerance: 8.5 [6.7-11.5], up from 6.4 [4.7-8.6]					
Non MTD: Loukopoulos, 1998 [41]	Post-HU (44) Pre-HU	Post-HU: 23.1 (9.2) Pre-HU: 6.7(4.7)		Post-HU: 9.3 Pre-HU: 8.9	Post-HU: 98.1 (15) Pre-HU 75.7 (11)				

Table 24. Outcome Data Stratified by Dosage in Adults (continued)

Study label	Study arm (N)	Hb F%*	%F cells*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Non MTD: Loukopoulos, 2000 [1]	Hb SS (14) Hb Sß0 thal (35) Hb Sß+ thal (20)	Hb SS: M: 28 (6.5), F: 26.6 (6.7) Hb Sß0 thal: M: 34.2 (12.8), F: 27.9 (14.3) Hb Sß+ thal: M: 25 (6.3), F: 25.2 (6.4)		Hb SS: M: 10.7 (0.8), F: 9.4 (1.5) Hb Sß0 thal: M: 9.8 (1.7), F: 8.8 (0.8) Hb Sß+ thal: M: 9.2 (1.7), F: 9.1 (1.1)	Hb SS M: 121.5 (17.3), F: 125.4 (8.3) Hb Sß0 thal: M: 100.4 (12.3) F: 100 (9.4) Hb Sß+ thal: M: 90.9 (11.1) F: 88.7 (12.4)				Mean clinical severity score of 81.7 over 12,018 pt-weeks was down from baseline score of 1182 (arbitrary scale). Outcomes measured at maximum HbF concentrations. HbF% difference was very significant (P < 0.001) in all but female HbSS pts. Hemoglobin difference was very significant (P < 0.001) only in male Hb Sß0 thal pts
Non MTD: Rigano, 2001[50]	Post-HU (22) Pre-HU	Post-HU: 25.2 (5.2)‡ Pre-HU: 7.5 (5.3)		Post-HU: 10 (1.5) Pre-HU: 6 (1.3)	Post-HU: 96.4 (7.2)‡ Pre-HU: 73.9	Post-HU: 10,200 (3,900) Pre-HU: 11,400 (3900)	Post-HU: 1.1 (1.8)/yr median = 0.5‡ Pre-HU: 7 /yr median = 9 (all crises including pain)	Post-HU: 0.5 (1.6)†; hospital days 1.2 (2.3) † Pre-HU: hospital days 22.4	

* Mean, (SD) [range] unless otherwise noted # p ≤ 0.005

† p ≤ 0.0001 **p = 0.0002

‡ p ≤ 0.001 ††p ≤ 0.00001 § p ≤ not significant ‡‡ p = 0.057 ‖ p ≤ 0.01 §§ Change from baseline ¶ p ≤ 0.002

ANC = absolute neutrophil count; CBT = cognitive based therapy; CSSCD = Cooperative Study of Sickle Cell Disease; Hb = hemoglobin; HbF = fetal hemoglobin; HTN = hypertension; HU = hydroxyurea; HUG-KIDS = Safety of Hydroxyurea in Children With Sickle Cell Anemia; LACA = left anterior cerebral artery; LMCA = left main coronary artery; LPCA = left posterior cerebral artery; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; NR = not reported; PHTN = pulmonary hypertension; pt-yr = patient-year; RACA = right anterior cerebral artery; RMCA = right middle cerebral artery; RPCA = right posterior cerebral artery; SCD = sickle cell disease; SD = standard deviation; TCD = transcranial Doppler; WBC = white blood cell; TRV: tricuspid regurgitant velocity; RVP: right ventricle pressure

Table 25. Outcome Data Stratified by Dosage in Children

Study label	Study arm (N)	Hb F%*	%F cells*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
MTD: Al-Jam'a, 2002[13]	Post-HU (27) Pre-HU	Post-HU: 25.7 (7.3) median = 25# Pre-HU: 12.6 (5.4)		Post-HU: 10.7 (1.4) median = 10.8# Pre-HU: 9.71 (1.2)		Post-HU: 6,260 (2,580) median 5,600# Pre-HU: 8,990 (3,480)	Pre-HU: 6.5/yr(2.8)	Post-HU: 0.93 (2.2) Median = 0†; hospital days 5.1 (13.5) median 0# Pre-HU: Hospital days 33.9 (26.1)	
MTD: de Montalembert, 1997[21]	Post-HU (35) Pre-HU (35)	Post-HU: 13.7 [3.2-27.0] † Pre-HU: 4 [0.8513.9]		Post-HU: 9 (1.4) p = 0.03 Pre-HU: 8.4 (1.2)					All but two patients had decreased frequency or termination of crises. No clear difference in weight or height velocity.
MTD: Flanagan, 2010[27]	HU (37)	Baseline Median = 5.9 MTD Median = 19.1		Baseline Median = 8.1 MTD Median = 9.1		Baseline Median = 12.4 MTD Median = 8.5			Red blood cell count (Baseline Median = 2.7 MTD Median = 2.5) Platelet count (Baseline Median = 495 MTD Median = 364) Absolute neutrophil count (Baseline Median = 5989 MTD Median = 3510) Absolute reticulocyte count (Baseline Median = 246 MTD Median = 126)
MTD: Hankins, 2005[31]	Post-HU (21) Pre-HU (21)	Post-HU: 23.7 (7.4)‡ Pre-HU: 21.8 (7.8)	Post-HU: 82.6 (7.9) ‡ Pre-HU: 80.6 (14.1)	Post-HU: 9.1 (1.4) ‡ Pre-HU: 8.5 (1.2)	Post-HU: 95.1 (10.4) ‡ Pre-HU: 81.7 (8.0)	Post-HU: 10,100 (5,000) ‡ Pre-HU: 12,600 (4,400)	Post-HU: 33.8/ 100 ptyr compared to 32.4/ 100 ptyr in CSSCD §		Outcomes are for 17 children after 4 years of therapy.
MTD: Hankins, 2007[32]	HU (52)								6 patients had recovery of splenic function; 24/25 had stable brain MRIs

Table 25. Outcome Data Stratified by Dosage in Children (continued)

Study label	Study arm (N)	Hb F%*	%F cells*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
MTD: Hankins, 2008[33]	HU (52)	Patients whom spleen function recovered or was preserved (Before HU = 9.3, During HU = 22.3) Patients whom Spleen function had no effect from HU (Before HU = 4.0, During HU = 18.2)	NR	Patients whom Spleen function recovered or was preserved (Before HU = 9.1, During HU = 11.1) Patients whom Spleen function had no effect from HU (Before HU = 8.6, During HU = 9.2)	Patients whom Spleen function recovered or was preserved (Before HU = 86 During HU = 104) Patients whom Spleen function had no effect from HU (Before HU = 86 During HU = 107)	Patients whom Spleen function recovered or was preserved (Before HU = 13.5 During HU = 8.7) Patients whom Spleen function had no effect from HU (Before HU = 15.9 During HU = 8.1)	NR	NR	Patients whom Spleen function recovered or was preserved (n = 8) Patients whom Spleen function had no effect from HU (n = 35) Patients whom brain function showed improvement on MRI (n = 24) Patients whom brain function worsened on MRI (n = 1) (patient had a new punctate hemorrhagic area in the right deep frontal white matter) Patients whom brain function was stable on MRA (n = 24) Patients whom brain function showed improvement on MRA (n = 1)
MTD: Kinney, 1999[37]	Post-HU (84) Pre-HU	Post-HU: 17.8 (7.2)† Pre-HU: 7.3	Post-HU: 66.5 (19.6) † Pre-HU: 34.6 (17.8)	Post-HU: 9 (1.4) † Pre-HU: 7.8	Post-HU: 101.3 (10.2) † Pre-HU: 85.9 (6.6)	Post-HU: 9,200 (3200) † Pre-HU: 13,600			Hematological effects were attained by 6 months (even before MTD). There was little difference between 6 and 12 month data. Continued weight gain and linear growth.
MTD: Kratovil, 2006[38]	HU (24) No HU	HU: 11.79, [3.8 - 25.4]†† relative to untreated		HU: 8.2 [5.2 - 10.6] ‡‡ relative to un-treated					HU: Mean of maximum TCD = 111.2 cm/sec No HU: Mean of maximum TCD = 124 cm/sec

Table 25. Outcome Data Stratified by Dosage in Children (continued)

Study label	Study arm (N)	Hb F%*	%F cells*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
MTD: Maier-Redelsperger, 1998[43]	Post-HU (29) Pre-HU (29)	Post-HU: 13 (9.4) Pre-HU: 4 [0.8513.9]	Post-HU: 54.2 (22.1) Pre-HU: 24.4	Post-HU: 9.1 (0.9) Pre-HU: 8.4 (1.2)	Post-HU: 101.8 (15.9) Pre-HU: 84.5				
MTD: Oliviere, 1998[47]	Post-HU (17) Pre-HU (17)	Post-HU: 16.7 (1.8) Pre-HU: 7.6 (1.6)		Post-HU: 10.2 (3.6) Pre-HU: 8.9 (4.3)	Post-HU: Post-HU: 104 (3) Pre-HU: 87 (7)		Post-HU: 1.2/yr (0.4) Pre-HU: 3.1/yr (0.5)	Post-HU: 1.7/yr (2.0) Pre-HU: 6.7/yr (2.8)	Acute chest syndrome rate declined from 1.3/yr to 0.2/yr. No difference in number of pitted red blood cells (n = 12 children) was observed.
MTD: Santos, 2002[51]	HU (21)	15.1§§							10 patients had improvement in splenic function
MTD: Thornburg, 2009[56]	HU (14)	25.9 (6.6)		9.5 (1)	99 (12)				
MTD: Thornburg, 2010[57]	HU (75)	8% inc' [6.2-9.8]		1.3 [1.0-1.5]					1699 cells/mm3 decrease in absolute neutrophil count
MTD: Ware, 2002[62]	Post-HU (68, 53 with sufficient data) Pre-HU	Post-HU: Median = 17.6, [2.9-32.4] Pre-HU: 6.7		Pre-HU: 7.7	Pre-HU: 85.7	Pre-HU: 14,000			HbF% was predicted by HbF% at baseline (p = .001) and Hb at baseline (p = 0.01); HbF% was negatively associated with # of pills returned (p = 0.02), postively with change in Hb (p < 0.0001), MCV (p = 0.01) and decline in reticulocytes (p = 0.01), and decline in white blood count (p = 0.006).
MTD: Ware, 2004[63]	HU (35)	18.6 (6.6)		9.2(1.4)	112(9)	7300 (2500)			Data collected on two groups; patients initiating HU after an abrupt halt to transfusion therapy, and patients initiating HU before transfusion therapy was completely halted. Pooled data was presented here. Stroke recurrence rate 5/7/100 pt-yrs (7 children, 4 of whom were noncompliant with HU).

Table 25. Outcome Data Stratified by Dosage in Children (continued)

Study label	Study arm (N)	Hb F%*	%F cells*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
MTD: Zimmerman, 2004[64]	Post-HU (122) Pre-HU (122)	Post-HU: 19.7 (8.5)‡ Pre-HU: 7.6		Post-HU: 9.7 (1.3) ‡ Pre-HU: 8.2	Post-HU: 105.8 (13.8) ‡ Pre-HU: 84.4 (8.5)	Post-HU: 7.0 Pre-HU: 12,400			Efficacy (in Hb, MCV, % Hb F, WBC count, ANC, reticulocyte, bilirubin) maintained over 7 years of follow-up
MTD: Zimmerman, 2007[65]	Patients with increased TCD velocities post HU (37) Patients with increased TCD velocities pre HU	Patients with increased TCD velocities post HU: 22.7 (7.9) median = 23.3 † Patients with increased TCD velocities pre HU: 10.3		Patients with increased TCD velocities post HU: 9.4 (1.1) median = 9.4 † Patients with increased TCD velocities pre HU: 7.8	Patients with increased TCD velocities post HU: 104 (9) median † Patients with increased TCD velocities pre HU: 86 (8)				Significant decline in TCD of RMCA, LMCA, RACA, LACA, and LPCA, but not RPCA. Stroke rate on treatment 0.52/100 ptyears, RMCA on treatment 134 cm/sec, p < .0001.
Non MTD: Bakanay, 2005[15]	HU (226)								Very little description of study population and treatment, also had concern about confounding by indication.
Non MTD: Dahoui, 2010[20]	Normal tricuspid regurgitant velocity (58) PHTN (27)								Pts on HU had a higher prevalence of PHTN and Hu was not able to stop PHTN from developing in 5 pts
Non MTD: Italia, 2009[2]	Children HbSS (25)	HbSS: 24.4 (6.3)	HbSS: 84.4 (10.8)	HbSS: 9.4 (1.9)	HbSS: 94.5 (10.6)	HbSS: 9.1 (3.4)	HbSS: 0-1/yr: 64% 2-3/yr: 36%	HbSS: None: 96% 1-2/yr: 4%	

Table 25. Outcome Data Stratified by Dosage in Children (continued)

Study label	Study arm (N)	Hb F%*	%F cells*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Non MTD: Odievre, 2008[46]	On HU and had vaso-occlusive events (26) Non HU and had vaso-occlusive events (20) Never had vaso-occlusive events (28) Non SCD (controls) (27)	On HU and had vaso-occlusive events: 11.6 Non HU and had vaso-occlusive events: 6.5 Never had vaso-occlusive events: 8.8 Non SCD (controls): 0.2		On HU and had vaso-occlusive events: 87 Non HU and had vaso-occlusive events: 79 Never had vaso-occlusive events: 80 Non SCD (controls): 129	On HU and had vaso-occlusive events: 87.6 Non HU and had vaso-occlusive events: 84.2 Never had vaso-occlusive events: 78.7 Non SCD (controls): 82.1				On HU and had vaso-occlusive events: PMN+++ 2.3, Platelets 246, Red blood cells 4.7, Reticulocytes 50.85, Hematocrit 39.9 non HU and had vaso-occlusive events: PMN 5.7, Platelets 478, Red blood cells 3.1, Reticulocytes 231.68, Hematocrit 4.7 Never had vaso-occlusive events: PMN 5.5, Platelets 434, Red blood cells 2.9, Reticulocytes 303.45, Hematocrit 24.3 Non SCD (controls): PMN 4, Platelets 431, Red blood cells 2.8, Reticulocytes 227.98, Hematocrit 26.6
Non MTD: Pashankar, 2008[48]	HU (6) Non HU (4)			HU: 7.98					HU: TRV and RVP decreased (40.16 to 23.6 mmHg) after 9-12 months of tx. O2 sat increased from 90 to 93%
Non MTD: Scott, 1996[53]	Post-HU (15) Pre-HU (15)	Post-HU: 15.2 (9.8,) [4.1-31] ¶ Pre-HU: 6.9 (6.2)		Post-HU: 9.5 (1.5) [7.7-13.1] Pre-HU: 8.2 (1.0)	Post-HU: 100 (15) [80-127] † Pre-HU: 85 (11)			Post-HU: 3/yr (4) Pre-HU: 7/yr(2.4)	
Non MTD: Svarch, 2006[55]	HU (51) Pre-HU (51)	HU: 12.4 (7.9) † Pre-HU: 6.4		HU: 8.5 (1) p = .0001 Pre-HU: 7.8		HU: 9,800 (2,100) p = 0.12 Pre-HU: 10,900	HU: Median 0.8/yr [0-2] Pre-HU: Median 3/yr	HU: 0.5 [04] Pre-HU: 4 [0-6]	HU: Resource-poor environment

Table 25. Outcome Data Stratified by Dosage in Children (continued)

Study label	Study arm (N)	Hb F%*	%F cells*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	Comments
Non MTD: Wang, 2001[61]	Post-HU (28) Pre-HU CSSCD	Post-HU: 20.3 (4.9) Pre-HU: 21.8 (7.8) CSSCD: 10.9 (7.9)	Post-HU: 76.2 (12.4) Pre-HU: 80.6 (14.1) CSSCD: 65.4 (11.2)	Post-HU: 8.8 (1.2) Pre-HU: 8.5 (1.2) CSSCD: 7.7 (1.0)	Post-HU: 90 (9.6) Pre-HU: 81.7 (8.0) CSSCD: 84.1 (10.1)	Post-HU: 10,100 (3,200) Pre-HU: 12600 (4,400) CSSCD: 14,300 (2,400)			Post-HU: Outcomes are for 21 patients who completed 2 years of treatment (not necessarily on MTD).

* Mean, (SD) [range] unless otherwise noted # p ≤ 0.005

† p ≤ 0.0001 **p = 0.0002

‡ p ≤ 0.001 ††p ≤ 0.00001 § p ≤ not significant ‡‡ p = 0.057 ‖ p ≤ 0.01 §§ Change from baseline ¶ p ≤ 0.002

ANC = absolute neutrophil count; CBT = cognitive based therapy; CSSCD = Cooperative Study of Sickle Cell Disease; Hb = hemoglobin; HbF = fetal hemoglobin; HTN = hypertension; HU = hydroxyurea; HUG-KIDS = Safety of Hydroxyurea in Children With Sickle Cell Anemia; LACA = left anterior cerebral artery; LMCA = left main coronary artery; LPCA = left posterior cerebral artery; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; NR = not reported; PHTN = pulmonary hypertension; pt-yr = patient-year; RACA = right anterior cerebral artery; RMCA = right middle cerebral artery; RPCA = right posterior cerebral artery; SCD = sickle cell disease; SD = standard deviation; TCD = transcranial Doppler; WBC = white blood cell; TRV: tricuspid regurgitant velocity; RVP: right ventricle pressure

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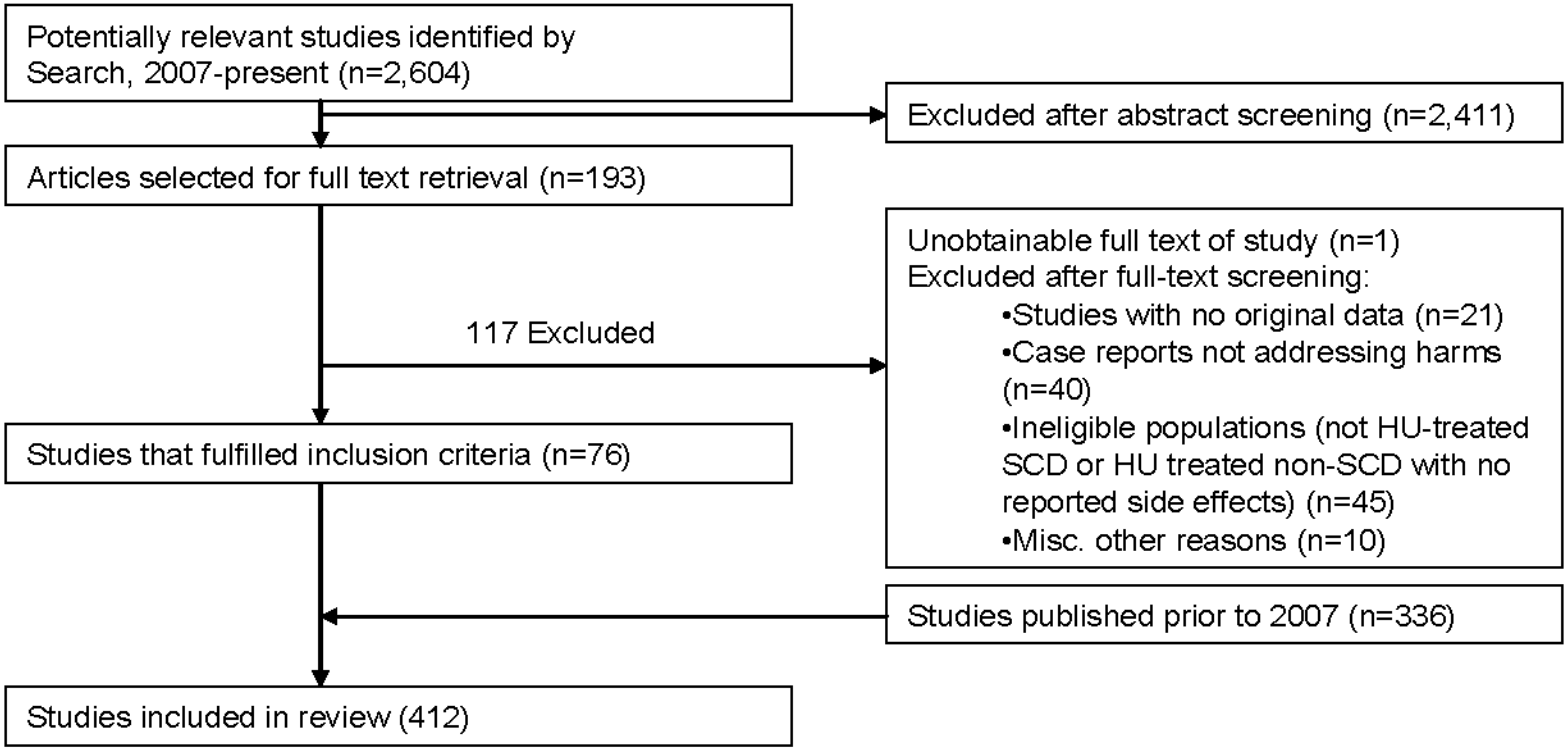
Appendix A. Selection Process



Appendix B. Search Strategy

EMBASE, Ovid MEDLINE(R), CCTR, CDSR

Number	Searches	Results
1	exp Anemia, Sickle Cell/	25696
2	(sickle cell or "hemoblobin s" or drepanocytemia or "drepanocytic anemia" or drepanocytosis or "hemoglobin ss" or meniscocytosis or "sickle anemia" or "ss disease").mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	29336
3	1 or 2	29430
4	thrombocythemia.mp. or exp Thrombocytosis/	9347
5	exp thrombocythemia/	5951
6	thrombocytosis.mp.	6949
7	4 or 5 or 6	10958
8	exp hydroxyurea/	17378
9	(biosupressin or hydrea or "hydroxy carbamid*" or "hydroxy urea" or hydroxycarbamid* or litalir or "nsc 32065" or oncocarbide or oxycarbamid* or oxyurea).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	673
10	8 or 9	17493
11	(3 or 7) and 10	2836
12	exp Drug Toxicity/	46407
13	exp Neoplasms/	3552247
14	exp Ulcer/	84952
15	exp Nausea/	102675
16	exp Alopecia/	28960
17	exp Safety/	138286
18	macrocytosis.mp.	1008
19	exp Gangrene/	9997
20	exp Erythema/	53632
21	myelosuppression.mp.	12055
22	exp Hyperpigmentation/	22762
23	(atrophy or scaling or rash or rashes).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	225030
24	exp Exanthema/	40375
25	exp Nail Diseases/ or melanonychia.mp.	15621
26	exp Keratosis/	28064
27	(keratosis or keratoses).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	15081
28	poikilodermat*.mp.	138
29	exp Telangiectasis/	15763
30	telangiectas*.mp.	20518
31	exp Polycythemia/ or polycythemia.mp.	15343
32	exp Dermatitis/ or dermatitis.mp.	140319

EMBASE, Ovid MEDLINE(R), CCTR, CDSR (continued)

Number	Searches	Results
33	lesion*.mp.	891820
34	exp Lichen Planus/	8726
35	(lichen adj2 planus).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	9939
36	exp Diarrhea/ or diarrhea.mp.	164704
37	constipation.mp. or exp Constipation/	48722
38	exp Anorexia/ or anorexia.mp.	56910
39	exp Vomiting/	93915
40	vomit*.mp.	148294
41	mucositis.mp. or exp Mucositis/	20234
42	exp Stomatitis/ or stomatitis.mp.	40713
43	exp Pancreatitis/ or pancreatitis.mp.	79457
44	leukopenia.mp. or exp Leukopenia/	113435
45	subarachnoid hemorrhage.mp. or exp Subarachnoid Hemorrhage/	32201
46	exp Fever/	99952
47	fever*.mp.	248249
48	azotemia.mp. or exp Azotemia/	11604
49	respiratory failure.mp. or exp Respiratory Insufficiency/	86802
50	exp Myelodysplastic Syndromes/	24786
51	Myelodysplastic Syndrome*.mp.	23046
52	exp Chromosome Aberrations/	191807
53	(abnormal* adj2 chromosome*).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	11612
54	reticulocytopenia.mp.	338
55	exp Hepatitis/	204588
56	hepatotoxicity.mp.	18399
57	systemic lupus erythematosus.mp. or Lupus Erythematosus, Systemic/	76250
58	drowsiness.mp. or exp Sleep Stages/	38115
59	exp Dizziness/	24491
60	(dizziness or dizzy).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	40333
61	exp Seizures/	80509
62	seizure*.mp.	162610
63	exp Headache/	97287
64	(headache* or migraine*).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	184185
65	peripheral neuropathy.mp. or exp Peripheral Nervous System Diseases/	135561
66	Blepharitis.mp. or exp Blepharitis/	2508
67	(flaky or flakiness).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	280
68	exp Confusion/	19786
69	(confusion or disorient*).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	48406

EMBASE, Ovid MEDLINE(R), CCTR, CDSR (continued)

Number	Searches	Results
70	exp Hallucinations/	21007
71	hallucinat*.mp.	26605
72	exp Cystitis/ or cystitis.mp.	19057
73	dysuria.mp. or exp Dysuria/	7057
74	exp Kidney Diseases/	641332
75	(kidney or renal).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	1144814
76	pulmonary fibrosis.mp. or exp Pulmonary Fibrosis/	36959
77	exp Lung Diseases, Interstitial/	59629
78	interstitial lung disease*.mp.	8645
79	exp Dyspnea/ or dyspnea.mp.	72682
80	exp Cough/ or cough.mp.	72130
81	exp Fetal Diseases/	90950
82	(fetal or maternal).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	557083
83	(toxicity or harm or "adverse event*" or neoplasm* or malignanc* or cancer* or ulcer* or nausea or vomit* or alopecia or "hair loss" or (delay* and (development* or growth)) or teratogen* or safety or leukemia* or gangrene or hyperpigmentation or Erythema or Exanthema or nail or nails or carcinoma*).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	4770421
84	or/12-83	8651154
85	10 and 84	12052
86	exp Hydroxyurea/to [Toxicity]	545
87	85 or 86	12182
88	exp Health Policy/	129475
89	(health adj2 policy).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	115896
90	exp Ethics/	194560
91	ethic*.mp.	176494
92	exp "Delivery of Health Care"/	1423835
93	(delivery adj2 "health care").mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	109544
94	exp Social Support/	59598
95	social support.mp.	69380
96	exp Psychology/	103885
97	psychology.mp.	261540
98	bias.mp.	113650
99	exp "Costs and Cost Analysis"/	288705
100	(cost or costs).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	580700
101	exp Health Behavior/	169022
102	health behavior*.mp.	47181
103	exp Communication/ or communication.mp.	607854
104	barrier*.mp.	207479

EMBASE, Ovid MEDLINE(R), CCTR, CDSR (continued)

Number	Searches	Results
105	patient satisfaction.mp. or exp Patient Satisfaction/	100829
106	comorbidity.mp. or exp Comorbidity/	126237
107	exp Depression/ or depression.mp.	449513
108	socioeconomic status.mp. or exp Social Class/	55564
109	social class.mp.	37828
110	social support.mp. or exp Social Support/	69380
111	family support.mp.	3716
112	exp Patient Education as Topic/	93519
113	education.mp. or exp Education/	969403
114	exp Insurance, Health/	163289
115	insurance.mp.	131371
116	exp "Quality of Health Care"/	4968725
117	(quality adj3 care).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	179772
118	practice pattern.mp.	582
119	disease severity.mp.	245657
120	burden.mp.	109792
121	cognitive ability.mp.	3681
122	respect.mp.	357536
123	exp Religion/	56517
124	(religion or religious).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, nm, ui, kw, tx, ct]	54626
125	exp Spirituality/	19416
126	spiritual*.mp.	13819
127	internal-external control.mp. or exp Internal-External Control/	222315
128	exp control/	208113
129	or/88-128	8374314
130	3 and 129	9336
131	11 or 87 or 130	21680
132	limit 131 to (meta analysis or "review") [Limit not valid in EMBASE,CDSR; records were retained]	4076
133	131 not 132	17604
134	"review"/	2509536
135	meta analysis/	63328
136	133 not 134 not 135	17517
137	limit 136 to english language [Limit not valid in CCTR,CDSR; records were retained]	16014
138	limit 137 to human [Limit not valid in CCTR,CDSR; records were retained]	14422
139	limit 138 to yr = "2007 -Current"	3210
140	limit 139 to humans [Limit not valid in CCTR,CDSR; records were retained]	3210
141	remove duplicates from 140	2514

Toxline

1. hydroxyurea or biosupressin or hydrea or "hydroxy carbamid*" or "hydroxy urea" or hydroxycarbamid* or litalir or "nsc 32065" or oncocarbide or oxycarbamid* or oxyuria
2. ("sickle cell" OR "hemoblobin s" OR drepanocytemia OR "drepanocytic anemia" OR drepanocytosis OR "hemoglobin ss" OR meniscocytosis OR "sickle anemia" OR "ss disease") and ((health and policy) OR ethic* OR (delivery and "health care") OR "social support" OR psychology OR bias OR cost OR costs OR "health behavior*" OR communication* OR barrier* OR "patient satisfaction" OR comorbidity OR depression OR "socioeconomic status" OR "social class" OR "social support" OR "family support" OR education OR insurance OR (quality and care) OR "practice pattern" OR "disease severity" OR burden OR "cognitive ability" OR respect OR religion OR religious OR spiritual* OR "internal-external control" OR control)
3. 1 or 2

Scopus

1. "sickle cell" OR "hemoblobin s" OR drepanocytemia OR "drepanocytic anemia" OR drepanocytosis OR "hemoglobin ss" OR meniscocytosis OR "sickle anemia" OR "ss disease"
2. thrombocythemia OR thrombocytosis
3. hydroxyurea OR biosupressin OR hydrea OR "hydroxy carbamid*" OR "hydroxy urea" OR hydroxycarbamid* OR litalir OR "nsc 32065" OR oncocarbide OR oxycarbamid* OR oxyuria
4. (1 or 2) and 3
5. toxicity OR harm OR "adverse event*" OR neoplasm* OR malignanc* OR cancer* OR ulcer* OR nausea OR vomit* OR alopecia OR "hair loss" OR (delay* AND (development* OR growth)) OR teratogen* OR safety OR leukemia* OR gangrene OR hyperpigmentation OR erythema OR exanthema OR nail OR nails OR carcinoma* OR macrocytosis OR myelosuppression OR atrophy OR scaling OR rash OR rashes OR melanonychia OR keratosis OR keratoses OR poikilodermat* OR telangiectas* OR polycythemia OR dermatitis OR lesion* OR (lichen W/2 planus) OR diarrhea OR constipation OR anorexia OR vomit* OR mucositis OR stomatitis OR pancreatitis OR leukopenia OR subarachnoid hemorrhage OR fever* OR azotemia OR respiratory failure OR "Myelodysplastic Syndrome*" OR (abnormal* W/2 chromosome*) OR reticulocytopenia OR hepatotoxicity OR hepatitis OR "systemic lupus erythematosus" OR drowsiness OR dizziness OR dizzy OR seizure* OR headache* OR migraine* OR "peripheral neuropathy" OR blepharitis OR flaky OR flakiness OR confusion OR disorient* OR hallucinat* OR cystitis OR dysuria OR kidney OR renal OR "pulmonary fibrosis" OR interstitial lung disease* OR dyspnea OR cough OR fetal OR maternal
6. 3 and 5
7. (health W/2 policy) OR ethic* OR (delivery W/2 "health care") OR "social support" OR psychology OR bias OR cost OR costs OR "health behavior*" OR communication* OR barrier* OR "patient satisfaction" OR comorbidity OR depression OR "socioeconomic status" OR "social class" OR "social support" OR "family support" OR education OR insurance OR (quality W/3 care) OR "practice pattern" OR "disease severity" OR burden OR "cognitive ability" OR respect OR religion OR religious OR spiritual* OR "internal-external control" OR control
8. 1 and 7
9. 4 or 6 or 8
10. Pubyear aft 2006
11. PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
12. (9 and 10) and not 11
13. review OR "meta-analy*" OR metaanaly*
14. 12 and not 13
15. Language(English)
16. 14 and 15

CINAHL

Search ID#	Search Terms	Search Options	Last Run Via	Results
S96	S3 and S94	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	52
S95	S3 and S94	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	490
S94	S76 or S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87 or S88 or S89 or S90 or S91 or S92 or S93	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	689251
S93	(MH "Spirituality")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	5987
S92	(MH "Religion and Religions+") or (MH "Religion and Psychology+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	16213
S91	(MH "Quality of Health Care+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	201066
S90	(MH "Insurance+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	49236
S89	(MH "Education+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	342622
S88	(MH "Patient Education+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	37847
S87	(MH "Social Class+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	3145
S86	(MH "Depression+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	30181
S85	(MH "Comorbidity")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	13671

CINAHL (continued)

Search ID#	Search Terms	Search Options	Last Run Via	Results
S84	(MH "Patient Satisfaction")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	17150
S83	(MH "Communication+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	82789
S82	(MH "Health Behavior+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	32006
S81	(MH "Costs and Cost Analysis+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	4030
S80	(MH "Psychology+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	716
S79	(MH "Support, Psychosocial+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	2850
S78	(MH "Health Care Delivery+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	15139
S77	(MH "Ethics+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	5749
S76	(MH "Health Policy+")	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	4505
S75	S3 and S73	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	54
S74	S3 and S73	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	54

CINAHL (continued)

Search ID#	Search Terms	Search Options	Last Run Via	Results
S73	(health N2 policy) OR ethic* OR (delivery N2 "health care") OR "social support" OR psychology OR bias OR cost OR costs OR "health behavior*" OR communication* OR barrier* OR "patient satisfaction" OR comorbidity OR depression OR "socioeconomic status" OR "social class" OR "social support" OR "family support" OR education OR insurance OR (quality N3 care) OR "practice pattern" OR "disease severity" OR burden OR "cognitive ability" OR respect OR religion OR religious OR spiritual* OR "internal-external control" OR control	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	84056
S72	S8 and S70	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	1
S71	S8 and S70	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	8
S70	S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	66664
S69	S8 and S67	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	0
S68	S8 and S67	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	14
S67	S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	18128
S66	S8 and S64	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	1
S65	S8 and S64	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	10
S64	S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	12532

CINAHL (continued)

Search ID#	Search Terms	Search Options	Last Run Via	Results
S63	S8 and S61	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	2
S62	S8 and S61	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	65
S61	S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	186749
S60	S8 and S10	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	4
S59	S8 and S10	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	116
S58	(s3 or s4 or s5) and s8	Limiters - Published Date from: 20070701-20101231; English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	4
S57	(s3 or s4 or s5) and s8	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	86
S56	(MH "Fetal Diseases+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S55	(MH "Cough")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S54	(MH "Dyspnea+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S53	(MH "Lung Diseases, Interstitial+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S52	(MH "Pulmonary Fibrosis")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

CINAHL (continued)

Search ID#	Search Terms	Search Options	Last Run Via	Results
S51	(MH "Kidney Diseases+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S50	(MH "Cystitis+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S49	(MH "Hallucinations")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S48	(MH "Confusion+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S47	(MH "Blepharitis")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S46	(MH "Peripheral Nervous System Diseases+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S45	(MH "Headache+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S44	(MH "Seizures+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S43	(MH "Dizziness")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S42	(MH "Lupus Erythematosus, Systemic+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S41	(MH "Hepatitis+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S40	(MH "Chromosome Abnormalities+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

CINAHL (continued)

Search ID#	Search Terms	Search Options	Last Run Via	Results
S39	(MH "Myelodysplastic Syndromes+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S38	(MH "Respiratory Failure+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S37	(MH "Uremia+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S36	(MH "Fever+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S35	(MH "Subarachnoid Hemorrhage")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S34	(MH "Leukopenia+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S33	(MH "Pancreatitis")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S32	(MH "Stomatitis+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S31	(MH "Mucositis")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S30	(MH "Vomiting+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S29	(MH "Anorexia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S28	(MH "Constipation")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

CINAHL (continued)

Search ID#	Search Terms	Search Options	Last Run Via	Results
S27	(MH "Diarrhea")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S26	(MH "Lichen Planus") or (MH "Lichen Planus, Oral")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S25	(MH "Dermatitis+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S24	(MH "Polycythemia")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S23	(MH "Telangiectasis+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S22	(MH "Keratosis+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S21	(MH "Nail Diseases+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S20	(MH "Exanthema")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S19	(MH "Hyperpigmentation+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S18	(MH "Erythema+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S17	(MH "Gangrene")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S16	(MH "Safety+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

CINAHL (continued)

Search ID#	Search Terms	Search Options	Last Run Via	Results
S15	(MH "Alopecia+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S14	(MH "Nausea")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S13	(MH "Ulcer")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S12	(MH "Neoplasms+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S11	(MH "Drug Toxicity+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S10	toxicity OR harm OR "adverse event*" OR neoplasm* OR malignanc* OR cancer* OR ulcer* OR nausea OR vomit* OR alopecia OR "hair loss" OR (delay* AND (development* OR growth)) OR teratogen* OR safety OR leukemia* OR gangrene OR hyperpigmentation OR erythema OR exanthema OR nail OR nails OR carcinoma* OR macrocytosis OR myelosuppression OR atrophy OR scaling OR rash OR rashes OR melanonychia OR keratosis OR keratoses OR poikilodermat* OR telangiectas* OR polycythemia OR dermatitis OR lesion* OR (lichen N2 planus) OR diarrhea OR constipation OR anorexia OR vomit* OR mucositis OR stomatitis OR pancreatitis OR leukopenia OR subarachnoid hemorrhage OR fever* OR azotemia OR respiratory failure OR "Myelodysplastic Syndrome*" OR (abnormal* N2 chromosome*) OR reticulocytopenia OR hepatotoxicity OR hepatitis OR "systemic lupus erythematosus" OR drowsiness OR dizziness OR dizzy OR seizure* OR headache* OR migraine* OR "peripheral neuropathy" OR blepharitis OR flaky OR flakiness OR confusion OR disorient* OR hallucinat* OR cystitis OR dysuria OR kidney OR renal OR "pulmonary fibrosis" OR interstitial lung disease* OR dyspnea OR cough OR fetal OR maternal	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

CINAHL (continued)

Search ID#	Search Terms	Search Options	Last Run Via	Results
S9	(s3 or s4 or s5) and s8	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S8	S6 or S7	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S7	hydroxyurea OR biosupressin OR hydrea OR "hydroxy carbamid*" OR "hydroxy urea" OR hydroxycarbamid* OR litalir OR "nsc 32065" OR oncocarbide OR oxycarbamid* OR oxyuria	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S6	(MH "Hydroxyurea")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S5	(MH "Thrombocytosis")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S4	thrombocythemia OR thrombocytosis	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S3	S1 or S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S2	"sickle cell" OR "hemoblobin s" OR drepanocytemia OR "drepanocytic anemia" OR drepanocytosis OR "hemoglobin ss" OR meniscocytosis OR "sickle anemia" OR "ss disease"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display
S1	(MH "Anemia, Sickle Cell+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	Display

Appendix C. Excluded Studies

List of Excluded Studies

Study Label	Title	Reason For Exclusion
Adewoye, 2007	Effectiveness of a dedicated day hospital for management of acute sickle cell pain	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Akar, 2008	Ten-year review of hospital admissions among children with sickle cell disease in Kuwait	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Alvarez, 2008	Short-term follow-up of patients with sickle cell disease and albuminuria	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Andaloussi, 2007	New complex chromosomal translocation in chronic myeloid leukaemia: T(9;18;22)(q34;p11;q11)	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Asnani, 2008	Quality of life in patients with sickle cell disease in Jamaica: rural-urban differences	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Aygun, 2009	Chronic transfusion practice for children with sickle cell anaemia and stroke	Other: no outcomes
Bachmeyer, 2008	Hydroxyurea for sickle cell anemia	Excluded because it is non original (i.e., review)
Barakat, 2007	A prospective study of the role of coping and family functioning in health outcomes for adolescents with sickle cell disease	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Barosi, 2007	A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group.[Erratum appears in Leukemia. 2007 May;21(5):1135]	Excluded because it is non original (i.e., review)
Beitler, 2007	Phase II clinical trial of parenteral hydroxyurea and hyperfractionated, accelerated external beam radiation therapy in patients with advanced squamous cell carcinoma of the head and neck: Toxicity and efficacy with continuous ribonucleoside reductase inhibition	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Boehm, 2009	Evaluation of in vivo antineoplastic effects of rapamycin in patients with chemotherapy-refractory AML	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Carobbio, 2007	Leukocytosis is a risk factor for thrombosis in essential thrombocythemia: Interaction with treatment, standard risk factors, and Jak2 mutation status	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Chakraborty, 2008	Joint Pain in AML: Successful Pain Control with Radiotherapy	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Chamberlain, 2008	Interferon-alpha for recurrent world health organization grade 1 intracranial meningiomas	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Chi, 2009	Hit or miss?	Excluded because it is non original (i.e., review)
Christoforidou, 2008	Hydroxyurea and anagrelide combination therapy in patients with chronic myeloproliferative diseases resistant or intolerant to monotherapy	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects

List of Excluded Studies (continued)

Study Label	Title	Reason For Exclusion
Citero, 2007	The role of catastrophizing in sickle cell disease--the PiSCES project	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Costa, 2007	Gene expression profiles of erythroid precursors characterize several mechanisms of the action of hydroxycarbamide in sickle cell anaemia	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Cotton, 2009	Religious/Spiritual coping in adolescents with sickle cell disease: a pilot study	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Dahabreh, 2007	Management of hypereosinophilic syndrome: a prospective study in the era of molecular genetics	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Dahdaleh, 2009	A "neurosurgical crisis" of sickle cell disease: Case report	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
DeBaun, 2010	Finally, a consensus statement on sickle cell disease manifestations: a critical step in improving the medical care and research agenda for individuals with sickle cell disease	Excluded because it is non original (i.e., review)
Dejmek, 2009	DNA-dependent protein kinase (DNA-PK)-dependent cisplatin-induced loss of nucleolar facilitator of chromatin transcription (FACT) and regulation of cisplatin sensitivity by DNA-PK and FACT	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Desjardins, 2007	Phase II study of imatinib mesylate and hydroxyurea for recurrent grade III malignant gliomas	Other: cannot separate tox from HU from other drugs
Drotar, 2010	Treatment adherence in patients with sickle cell anemia	Excluded because it is non original (i.e., review)
Dubowy, 2008	Sequential oral hydroxyurea and intravenous cytosine arabinoside in refractory childhood acute leukemia: a pediatric oncology group phase 1 study	Other: toxicity reported was due to ara-c not HU
Erb, 2008	Primary Amenorrhea in a Young Adult with Sickle Cell Disease: A Case Report and Brief Literature Review on Adolescent Reproductive Health and Sickle Cell Disease	Excluded because it is non original (i.e., review)
Erba, 2009	Prognostic factors in elderly patients with myelodysplastic syndrome or acute myeloid leukemia and the implications for treatment	Excluded because it is non original (i.e., review)
Farra, 2010	Vascular at-risk genotypes and disease severity in Lebanese sickle cell disease patients	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Fitzhugh, 2010	Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Friedman, 2008	Case 1: An unusual cause of headaches and priapism in a teenager	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Gaudreau, 2009	Treatment with hydroxyurea in a patient compound heterozygote for a high oxygen affinity hemoglobin and beta-thalassemia minor	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Ghatpande, 2008	Pharmaco-proteomic study of hydroxyurea-induced modifications in the sickle red blood cell membrane proteome	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects

List of Excluded Studies (continued)

Study Label	Title	Reason For Exclusion
Ghatpande, 2010	In vivo pharmaco-proteomic analysis of hydroxyurea induced changes in the sickle red blood cell membrane proteome	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Girodon, 2008	Frequent reduction or absence of detection of the JAK2-mutated clone in JAK2V617F-positive patients within the first years of hydroxyurea therapy	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Gosavi, 2009	Atrial septal defect closure on cardiopulmonary bypass in a sickle cell anemia: role of hydroxyurea and partial exchange transfusion	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Goto, 2009	Chronic neutrophilic leukemia with congenital Robertsonian translocation successfully treated with allogeneic bone marrow transplantation in a young man	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Grace, 2010	Resolution of cerebral artery stenosis in a child with sickle cell anemia treated with hydroxyurea	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Hall, 2008	Treatment of recalcitrant disseminated granuloma annulare with hydroxyurea	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Hankins, 2007	Therapy preference and decision-making among patients with severe sickle cell anemia and their families	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Hankins, 2008	Phase I study of magnesium pidolate in combination with hydroxycarbamide for children with sickle cell anaemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Harousseau, 2009	A randomized phase 3 study of tipifarnib compared with best supportive care, including hydroxyurea, in the treatment of newly diagnosed acute myeloid leukemia in patients 70 years or older	Other: no outcomes
Hernigou, 2009	Septic Arthritis in Adults with Sickle Cell Disease Often is Associated with Osteomyelitis or Osteonecrosis	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Hildreth, 2008	Sickle cell vasculopathy	Excluded because it is non original (i.e., review)
Howard, 2007	Treatment for children with severe aplastic anemia and sickle cell disease in low income countries in Latin America: a report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO): Part III	Excluded because it is non original (i.e., review)
Irfan, 2009	Clinico-pathological features and outcomes in chronic phase chronic myeloid leukemia patients treated with hydroxyurea	Other: no outcomes
Italia, 2010	Exposure to hydroxyurea during pregnancy in sickle-beta Thalassemia: A report of 2 cases	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Janot, 2008	Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Karimi, 2009	Echocardiographic finding in beta-thalassemia intermedia and major: Absence of pulmonary hypertension following hydroxyurea treatment in beta-thalassemia intermedia	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Karimi, 2010	Effect of combination therapy of hydroxyurea with l-carnitine and magnesium chloride on hematologic parameters and cardiac function of patients with beta-thalassemia intermedia	Other: no outcomes, all 4 groups received HU

List of Excluded Studies (continued)

Study Label	Title	Reason For Exclusion
Kurabayashi, 2007	Delayed manifestation and slow progression of cerebral infarction caused by polycythemia rubra vera	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Lanaro, 2009	Altered levels of cytokines and inflammatory mediators in plasma and leukocytes of sickle cell anemia patients and effects of hydroxyurea therapy	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Lanzkron, unkown year	Examining the effectiveness of hydroxyurea in people with sickle cell disease	Unobtainable full text
Levenson, 2008	Depression and anxiety in adults with sickle cell disease: the PiSCES project	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Li, 2008	The negative prognostic impact of derivative 9 deletions in patients who received hydroxyurea treatment for chronic myelogenous leukemia in the chronic phase	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Liao, 2007	Unnatural amino acid-substituted (hydroxyethyl)urea peptidomimetics inhibit gamma-secretase and promote the neuronal differentiation of neuroblastoma cells	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Linardi, 2008	Diagnosis and treatment of polycythemia vera: Brazilian experience from a single institution	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Lukusa, 2008	Use of hydroxyurea from childhood to adult age in sickle cell disease: semen analysis	Excluded because it is non original (i.e., review)
Ma, 2007	Fetal hemoglobin in sickle cell anemia: genetic determinants of response to hydroxyurea	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Machtay, 2008	Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: An RTOG analysis	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Masera, 2007	Periodic erythroexchange is an effective strategy for high risk pediatric patients with sickle-cell disease	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Mayor, 2008	UK enquiry shows lack of knowledge about complications in patients with sickle cell disease	Excluded because it is non original (i.e., review)
Meo, 2008	Effect of hydroxyurea on extramedullary haematopoiesis in thalassaemia intermedia: Case reports and literature review	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Miller, 2010	Urine concentrating ability in infants with sickle cell disease: baseline data from the phase III trial of hydroxyurea (BABY HUG)	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Mizutani, 2010	Emergence of chronic myelogenous leukemia during treatment for essential thrombocythemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
NA, 2008	Sickle cell protocol helps patients' self-management	Excluded because it is non original (i.e., review)
NA, 2008	Summaries for patients. Pain and health care visits in patients with sickle cell disease	Excluded because it is non original (i.e., review)
Naina, 2008	Hydroxyurea for sickle cell anemia	Excluded because it is non original (i.e., review)

List of Excluded Studies (continued)

Study Label	Title	Reason For Exclusion
Nand, 2008	Hydroxyurea, azacitidine and gemtuzumab ozogamicin therapy in patients with previously untreated non-M3 acute myeloid leukemia and high-risk myelodysplastic syndromes in the elderly: results from a pilot trial	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Nozaki, 2010	Hydroxyurea as an inhibitor of hepatitis C virus RNA replication	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
O'Brien 2009	Decision analysis of treatment strategies in children with severe sickle cell disease	Excluded because it is non original (i.e., review)
O'Keeffe, 2009	A patient with a previous diagnosis of hemoglobin S/C disease with an unusually severe disease course	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Olnes, 2009	Improvement in hemolysis and pulmonary arterial systolic pressure in adult patients with sickle cell disease during treatment with hydroxyurea	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Patra, 2010	Chronic idiopathic myelofibrosis with myeloid metaplasia presenting as refractory ascites	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Platt, 2008	Hydroxyurea for the treatment of sickle cell anemia	Excluded because it is non original (i.e., review)
Rahim, 2008	Diagnosis and treatment of cord compression secondary to extramedullary hematopoiesis in patients with beta-thalassemia intermedia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Reardon, 2009	Multicentre phase II studies evaluating imatinib plus hydroxyurea in patients with progressive glioblastoma	Other: adverse effects were not clearly related to HU
Reardon, 2009	Phase I pharmacokinetic study of the vascular endothelial growth factor receptor tyrosine kinase inhibitor vatalanib (PTK787) plus imatinib and hydroxyurea for malignant glioma	Other: both groups received HU and adverse effects are not attributable to HU
Rodzaj, 2009	A diagnostically difficult case of chronic myeloid neoplasm with eosinophilia and abnormalities of PDGFRA effectively treated with imatinib in accelerated phase	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Rose, 2007	Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Schwalenstocker, 2009	Appropriate use of quality measures: Response to "Risk factors for hospital readmission within 30 days: A new quality measure for children with sickle cell disease"	Excluded because it is non original (i.e., review)
Schwarz, 2009	A 62-year-old woman with bilateral pleural effusions and pulmonary infiltrates caused by extramedullary hematopoiesis	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Scott, 2010	Hydroxyurea and sickle cell disease: Its been a long, long time coming	Excluded because it is non original (i.e., review)
Sedrak, 2009	A prospective appraisal of pulmonary hypertension in children with sickle cell disease	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Seiwert, 2007	A phase I trial of docetaxel based induction and concomitant chemotherapy in patients with locally advanced head and neck cancer	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects

List of Excluded Studies (continued)

Study Label	Title	Reason For Exclusion
Seiwert, 2008	Phase I study of bevacizumab added to fluorouracil- and hydroxyurea-based concomitant chemoradiotherapy for poor-prognosis head and neck cancer	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Seth, 2009	Successful use of terbutaline in persistent priapism in a 12-year-old boy with chronic myeloid leukemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Setty, 2009	Prolonged chronic phase of greater than 10 years of chronic myelogenous leukemia in a patient with congenital human immunodefeciency virus infection	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Shah, 2007	Myelosuppression in patients benefiting from imatinib with hydroxyurea for recurrent malignant gliomas	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Singer, 2008	Hydroxycarbamide-induced changes in E/beta thalassemia red blood cells	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Singh, 2008	Resolution of chronic hypoxemia in pediatric sickle cell patients after treatment with hydroxyurea	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Smith, 2008	Daily assessment of pain in adults with sickle cell disease	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Smith, 2009	Climatic and geographic temporal patterns of pain in the Multicenter Study of Hydroxyurea	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Snyder, 2009	Therapeutic doses of hydroxyurea cause telomere dysfunction and reduce TRF2 binding to telomeres	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Sodani, 2010	Purified T-depleted, CD34+ peripheral blood and bone marrow cell transplantation from haploidentical mother to child with thalassemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Solomon, 2008	Treatment and prevention of pain due to vaso-occlusive crises in adults with sickle cell disease: an educational void	Excluded because it is non original (i.e., review)
Soutou, 2009	Myeloproliferative disorder therapy: Assessment and management of adverse events - A dermatologist's perspective	Excluded because it is non original (i.e., review)
Spencer, 2008	Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck	Other: cannot attribute toxicity to HU
Stagno, 2009	Uncommon long-term survival in a patient with chronic myeloid leukemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Sugino, 2009	Miliary tuberculosis associated with chronic neutrophilic leukemia	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Suliman, 2009	Hydroxyurea or chronic exchange transfusions in patients with sickle cell disease: role of transcranial Doppler ultrasound in stroke prophylaxis	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Takahashi, 2007	Epstein-Barr virus-associated post-transplant lymphoproliferative disorder presenting with skin involvement after CD34-selected autologous peripheral blood stem cell transplantation	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)

List of Excluded Studies (continued)

Study Label	Title	Reason For Exclusion
Thompson, 2010	The pediatric hydroxyurea phase III clinical trial (BABY HUG): challenges of study design	Excluded because it is non original (i.e., review)
Tomson, 2007	Hydroxycarbamide: a treatment for lichen sclerosus?	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Trelinski, 2009	The influence of low-dose aspirin and hydroxyurea on platelet-leukocyte interactions in patients with essential thrombocythemia	Other: cannot separate HU effect from ASA
Tsikrikas, 2008	Acute splenic sequestration crisis (ASSC) in an adult patient with beta-thalassemia sickle cell disease: a life-threatening complication	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Tufan, 2007	Spinal epidural extramedullary hematopoiesis during the complicated course of polycythemia vera	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Tutaeva, 2007	Application of PRV-1 mRNA expression level and JAK2V617F mutation for the differentiating between polycytemia vera and secondary erythrocytosis and assessment of treatment by interferon or hydroxyurea	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Tybura, 2009	The influence of low-dose aspirin and hydroxyurea on platelet-leukocyte interactions in patients with essential thrombocythemia	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
van den Tweel, 2008	Quality of life of female caregivers of children with sickle cell disease: a survey	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
van Tuijn, 2010	Acute chest syndrome in sickle cell disease due to the new influenza A (H1N1) virus infection	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Varma, 2008	Thrombotic complications of polycythemia vera	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Voskaridou, 2007	Pulmonary hypertension in patients with sickle cell/beta thalassemia: incidence and correlation with serum N-terminal pro-brain natriuretic peptide concentrations	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Wang, 2010	Summary of 615 patients of chronic myeloid leukemia in Shanghai from 2001 to 2006	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Ware, 2010	Renal Function in Infants with Sickle Cell Anemia: Baseline Data from the BABY HUG Trial	Excluded because it does not describe patients who used HU or describes non SCD patients who used HU but no reported side effects
Yates, 2009	Simultaneous acute splenic sequestration and transient aplastic crisis in children with sickle cell disease	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)
Zhang, 2007	Modified conditioning regimen busulfan-cyclophosphamide followed by allogeneic stem cell transplantation in patients with multiple myeloma	Excluded because it is a case report that does not address harms (case reports are only included if they report harm)